NASA Contractor Report 3707

Research Opportunities in Cardiovascular Deconditioning

Final Report Phase I

CONTRACT NASW-3616
JULY 1983

25th Anniversary
1958-1983

NASA

NASA Contractor Report 3707

Research Opportunities in Cardiovascular Deconditioning

Final Report Phase I

M. N. Levy and J. M. Talbot, *Editors*
Federation of American Societies for Experimental Biology
Bethesda, Maryland

Prepared for
NASA Office of Space Science and Applications
under Contract NASW-3616

National Aeronautics
and Space Administration

**Scientific and Technical
Information Branch**

1983

FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

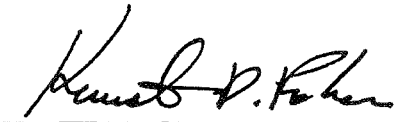
This technical report was developed for the National Aeronautics and Space Administration (NASA) in accordance with the provisions of Contract NASW 3616. It was prepared and edited by Matthew N. Levy, M.D., Chief of Investigative Medicine, the Mt. Sinai Medical Center, Cleveland, Ohio, who served as Key Biomedical Scientist for this effort and John M. Talbot, M.D., Senior Medical Consultant, LSRO.

The LSRO acknowledges the contributions of the investigators and consultants who assisted with this study. The report reflects the opinions expressed by an ad hoc study group that met at the Federation on July 6-7, 1982. The study participants reviewed a draft of the report and their various viewpoints were incorporated into the final report. The study participants and LSRO accept responsibility for the accuracy of the report; however, the listing of these individuals in Section VIII does not imply that they specifically endorse each study conclusion.

The report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to NASA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

February 25, 1983
(date)



Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office

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SUMMARY

One of the unresolved biomedical problems of space flight is a lack of means to prevent or control the "deconditioning" of the cardiovascular system that occurs during "adaptation" to the environmental influences of space flight. Evidence of cardiovascular deconditioning obtained directly from observations of astronauts and cosmonauts during flight and postflight has accumulated since it was first reported following the 9-hour Mercury mission. Since completion of the Skylab space flight program in 1974, substantial amounts of additional data on the cardiovascular effects of long orbital flights and ground-based simulation studies have been reported. Although human adaptability to the space flight environment appears adequate for missions lasting at least 6 months, important unresolved questions persist.

In order to ensure crew safety and mission accomplishment in future manned space programs, NASA needs more precise data on the nature and mechanisms of cardiovascular adaptation and deconditioning that result from exposure to the space flight environment, in particular to weightlessness, the dimensions and practical significance of possible regressive changes in the myocardium and other parts of the cardiovascular system, and the most efficient methods of preventing or treating functional and possible organic deterioration of the cardiovascular system.

Mechanisms of cardiovascular deconditioning

The basic cause of the cardiovascular deconditioning response is generally agreed to be weightlessness, which results in disappearance of the customary, gravity-induced, hydrostatic pressure gradients throughout the body. Immediately upon exposure to zero-G a shift in regional blood volumes occurs towards the most compliant segments of the circulation, i.e. the lungs, heart and the systemic veins, which are only partially filled when at 1-G. This regional volume change is presumably followed by a change in total blood volume caused by transcapillary fluid movements consequent to the elimination of gravitationally induced intravascular and tissue pressure gradients. In a gravitational-force environment such as that on planet Earth, such gradients are present in all body positions and are proportional to the differences in vertical height of the various capillary beds in the systemic and pulmonary circulations associated with any particular body position. Suppression of vasopressin release accompanied by a water diuresis and natriuresis are characteristic responses early in simulated weightlessness, and have been postulated in zero-G.

While the exact biologic mechanisms of the deconditioning response subsequent to the rapid changes in regional blood volume and increase in right atrial filling pressure, which are presumed to occur at the onset of the zero-G environment, have not been established, several possible hypotheses are either under investigation or included in future research plans. These suggest: (1) a decrease in overall blood volume subsequent to the presumed increase in central venous pressure which occurs concomitantly with the onset of the zero-G environment, (2) changes in shape and position of the diaphragm and associated changes in lung volume, (3) altered cardiac output and redistribution of systemic and pulmonary blood flow and ventilation, (4) changes in venous compliance and/or capacity, (5) possible changes in reflex control of cardiovascular function, (6) changes in the densities and sensitivities of cardiovascular volume, pressure and neurohumoral receptors, (7) altered peripheral sympathetic function and decreased adrenergic responsiveness of vascular smooth muscle, (8) impaired release or uptake of norepinephrine, (9) relative disuse of the lower extremities with loss of muscle pumping, and (10) increased intracranial pressure leading to changes in control and production of central nervous system regulatory hormones. In addition, possible interactive effects on the cardiovascular system of abnormal environmental responses of other organ systems and regulatory functions may be significant.

Countermeasures

Attempts to prevent or control cardiovascular deconditioning have involved inflight, reentry, and postflight measures as well as experimental interventions during or after bed rest and other ground-based analogues of weightlessness. These measures have included inflight exercises and lower body negative pressure (LBNP), venous occlusion, pre-reentry fluid and electrolyte replacement, use of anti-G suits during and following reentry, and postflight supportive measures. In addition, drugs and hormones have been tested experimentally.

Expert opinion is divided about the extent of protection offered by such measures as vigorous, regularly scheduled exercise, repeated LBNP, and pre-reentry fluid and electrolyte replacement. However, from experience with long-term manned flights, Soviet investigators are sufficiently convinced of the efficacy of such measures that they consider their inclusion during long-term missions mandatory. However, some investigators regard such countermeasures as marginally effective or noneffective in preventing the cardiovascular deconditioning, particularly the orthostatic intolerance, associated with weightlessness or its ground-based models.

In spite of variable and sometimes contradictory results obtained during studies of countermeasures, certain approaches have appeared promising enough to warrant further research and development. Among these are dynamic exercise, static exercise, centrifugation, prolonged LBNP stressing (4 h/d) combined with oral replacement of fluids, and the use of anti-G suits or leotards.

Program assessment

The primary task in this review was evaluation of NASA's ground-based research and technology program and identification of opportunities for its improvement. One question of fundamental importance is whether the biologic responses to the currently available methods of simulating zero-G truly represent the effects of weightlessness. One of the experts in the ad hoc Group firmly believes that none of the ground-based models provides an adequate simulation of the circulatory and subsequent effects of the agravic environment (see Appendix). However, a majority of the study participants regarded ground-based analogues of weightlessness as useful approaches to the study of the general problems of cardiovascular deconditioning and the most feasible approach for controlled experiments with statistically significant numbers of subjects. With the caveat regarding validation of the ground-based models by inflight study, NASA's current and planned program of ground-based research is well formulated to accomplish its objectives. However, the level of effort needs selective augmentation to expedite the resolution of certain aspects of the problem.

Critical questions and suggested research

Questions deserving high priority concern: (1) whether degenerative changes occur in the cardiovascular system during medium- and long-term missions, in particular, a possible loss of myocardial mass, (2) the nature and temporal development of changes in cardiovascular regulatory control mechanisms, (3) possible changes in the density and sensitivity of the pressure, volume, and neurohumoral receptors in the cardiovascular system, (4) alterations in vascular compliance and capacity, (5) associated changes in hemodynamics, and (6) the nature of the redistributed blood flows.*

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* One member of the LSRO ad hoc Working Group suggested that this paragraph required altered emphasis (see Appendix, p.63).

In order to facilitate the investigation of these problems, the state-of-the-art in methodology and instrumentation needs substantial improvement. For instance, improved means are needed for measuring non-invasively, in living subjects, such characteristics as cardiopulmonary dimensions, heart chamber volumes, and myocardial mass. Current methods for in vivo functional assessment of cardiovascular mechanoreceptors must be improved as should methods for measuring absolute changes in venous volume. Greater attention should be given to the selection of the most suitable animal models and to the design of animal experiments in such a way as to eliminate, if possible, spurious influences that may result from equipment and methodology employed. Finally, computer and other models of the cardiovascular system offer possible improvements in experimental design despite the lack of complete, explicit data on the basic mechanisms of cardiovascular deconditioning.

Conclusions

The cumulative experience from manned space flight suggests that the effects on the cardiovascular system are tolerable and reversible, and do not interfere with inflight crew effectiveness during missions lasting six or seven months. Postflight orthostatic intolerance has occurred after all manned flights to date, requiring supportive care to prevent possible injuries and to aid in the process of readapting to Earth gravity. Whether space missions of greater duration than heretofore will cause more profound changes in the integrity of the cardiovascular system is unknown. However, in view of the future likelihood of longer manned missions, and until such time as a reliable understanding of the basic mechanisms of cardiovascular deconditioning is acquired and effective, practical countermeasures have been developed and proved, the ad hoc Working Group on Cardiovascular Deconditioning suggests that the NASA ground-based research and technology program in cardiovascular deconditioning, reinforced where feasible by incorporation of the suggestions contained in this report, should be given a high priority in NASA's research and technology plans.

TABLE OF CONTENTS

		Page
	Foreword	iii
	Summary	v
I.	Introduction	1
II.	Objectives and Scope of the Study	3
III.	Overview of Cardiovascular Deconditioning	5
	A. Definition	5
	B. Cardiovascular Responses to Weightlessness and Simulated Weightlessness	8
	C. Countermeasures	14
	D. Related Factors and Physiologic Functions	20
IV.	NASA's Program of Ground-Based Research in Cardiovascular Deconditioning	23
V.	Observations of the ad hoc Working Group on Cardiovascular Deconditioning	25
	A. Hemodynamic Factors	25
	B. Effects of Space Flight on Cardiovascular System Receptors	30
	C. Catabolic, Atrophic, and Histopathologic Changes	32
	D. Hormonal and Neurohumoral Factors	34
	E. Countermeasures	35
	F. Methodology	38
VI.	Proposed Priorities of Suggested Research and Analysis	41
VII.	Literature Cited	47
VIII.	Study Participants	59

Page

IX. Appendix 61

Minority Opinion 63

A. Alterations to page vii of the summary 63

B. Alterations to page 10 of the subsection on cardiovascular responses to simulated weightlessness 63

C. Additions to page 41 of the section on proposed research priorities 67

D. Supporting literature citations for the minority opinion 67

I. INTRODUCTION

The record of achievement in manned space flight has been magnificent and nearly faultless. The experiences of both the United States and the Soviet Union have demonstrated man's adaptability to the effects of the space environment for exposures as long as 6 months without serious untoward medical effects (Soffen and Gazenko, 1981).

However, significant physiologic changes do occur even in relatively brief space flights measured in hours or days. A "deconditioning" of the cardiovascular system is one important complex of responses that results in remarkable, but transitory, functional impairment of spacecrews immediately following return to Earth (Berry, 1974; Berry et al., 1966; Dietlein, 1977; Kalinichenko et al., 1976; Pestov and Geratewohl, 1975; Sandler, 1980; Vorob'yev et al., 1976). The functional impairment caused by the deconditioning process is manifested primarily by orthostatic intolerance when the subject assumes the upright posture. The resultant signs and symptoms of cardiovascular instability include tachycardia, labile arterial blood pressure, narrowed pulse pressure, presyncopal symptoms, and syncope. It impairs other functions as well, such as work capacity and maximal oxygen uptake during exercise.

While the range of time for return of cardiovascular functions to preflight values has typically varied between 2 and 5 days, one member of the crew of Apollo 15 required 13 days, and, after one of the Soviet missions, full recovery of the cosmonauts required as long as 30 days (Sandler, 1980). Such delayed recoveries have not always been directly related to mission duration. Critical questions have arisen on how long an astronaut can continue to function efficiently and maintain acceptable physiologic status inflight and whether any of the adaptive changes that characterize cardiovascular deconditioning may become irreversible. A more immediate question is whether the accelerative stress of reentry exposure to 1.5 G for up to 20 minutes will pose any hazard to Shuttle crews, whose times aloft will probably not exceed 2 weeks. Ultimately, the biomedical feasibility of future manned missions lasting for a year should be determined as a logical goal in probing the effects of more prolonged space missions.

Thus, in order to ensure crew safety and effectiveness, NASA requires more knowledge of (a) the nature and mechanisms of cardiovascular adaptation and deconditioning that result from the influence of weightlessness, (b) the occurrence, dimensions, and practical significance of the possible regressive changes in the myocardium and other parts of the cardiovascular system, and (c) the most efficient methods of preventing or treating functional or organic deterioration of the cardiovascular system, if this does occur.

NASA requested that the Life Sciences Research Office of the Federation of American Societies for Experimental Biology review and evaluate available knowledge and ongoing research and provide additional scientific input for future research programming on cardiovascular deconditioning. This has been done with the assistance of an ad hoc Working Group of outstanding scientists, supplemented by other prominent investigators, who are identified in Section VIII.

II. OBJECTIVES AND SCOPE OF THE STUDY

The objectives of the LSRO study of the problem of cardiovascular deconditioning associated with space flight are:

(1) to review extant information on the subject;

(2) to examine NASA's current and projected research program;

(3) to identify significant gaps, if any, in essential knowledge;

(4) to formulate suggestions to NASA for future research; and,

(5) to produce a documented report of the foregoing items that can be used for NASA program planning for future research.

The main emphasis in this report, in accordance with NASA's guidelines, is on the ground-based research and technology development program on cardiovascular deconditioning. This does not imply that the LSRO ad hoc Working Group on Cardiovascular Deconditioning regards the inflight research and development program as secondary in importance. In fact, one of the participants is convinced that the full relevance of ground-based studies relative to space flight cannot be assessed until information concerning the magnitude and time course of changes in right atrial pressure in humans during space flight has been obtained.

The main sources of information for the study include (a) the scientific and technical literature, (b) unpublished data from the United States and Soviet space programs, (c) the NASA Research and Technology Objectives and Plans (RTOPs), and (d) Research and Technology Resumes (RTRs) on cardiovascular deconditioning and related biomedical problems of space flight. Examples of topics reviewed in the field of the effects of weightlessness and its terrestrial analogues on cardiovascular physiology include hemodynamics, cardiovascular adaptation and function, venous compliance, control mechanisms, orthostatic hypotension, patterns of postflight readaptation, countermeasures, and methodology for tests, analyses, and measurements. In addition, the influence of other organ systems and homeostatic mechanisms on cardiovascular adaptation and deconditioning is considered where appropriate.

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III. OVERVIEW OF CARDIOVASCULAR DECONDITIONING

This section presents a synopsis of well established knowledge and certain key issues concerning the responses of the cardiovascular system to real and simulated weightlessness. Only a small part of the pertinent literature is cited. Additional information is available in other reports, compendia, reviews, and thematic publications, such as: Berry, 1970, 1973; Blomqvist and Stone, 1983; Bricker, 1979; Busby, 1967; Calvin and Gazenko, 1975; Gazenko et al.,1981; Genin and Egorov, 1981; Howard, 1965; International Union of Physiological Sciences, 1979, 1980, 1981; Johnston and Dietlein, 1977; McCally, 1968; Parrin et al., 1970; Pestov and Geratewohl, 1975; Roth, 1968; Sandler, 1980; Soffen and Gazenko, 1981; Vasil'yev and Kotovskaya, 1975; Whedon, 1978.

A. DEFINITION

The cardiovascular deconditioning that is associated with exposure to space flight is said to be an adaptive process that begins very shortly after entry into orbit. It features a headward shift of blood and body fluids, vascular congestion of the head and neck, a reduction in total blood volume, and changes in the physiologic mechanisms that are necessary for maintaining adequate circulation and consciousness while an individual is upright in the 1-G environment (Whedon, 1978). These changes have been described as adaptive to null gravity, nonimpairing in terms of crew performance and health, and they stabilize after 4 to 6 weeks of weightlessness (Dietlein, 1977). Although tolerance to lower body negative pressure (LBNP) during spaceflight declines, relative to preflight values, inflight exercise capacity appears to be preserved (Genin and Egorov, 1981; Michel et al., 1977), suggesting that the adaptive changes in the cardiovascular system are appropriate to the weightless environment. On return to Earth, however, when the subject is in the vertical position, orthostatic intolerance occurs, including tachycardia, narrowed pulse pressure, and hypotension, sometimes resulting in presyncope or frank syncope (Sandler, 1980). Postflight impairment of locomotion and reduction of exercise tolerance are also common. These, and other effects on the cardiovascular system resembling those that are associated with weightlessness, have been produced as well in ground-based studies employing bed rest, chair rest, or immersion in water as means of simulating weightlessness (Sandler, 1980).

Table 1 lists the principal cardiovascular findings of the nine astronauts in Skylab missions 2, 3, and 4 (lengths of flight were 28, 59, and 84 days, respectively). Table 2 shows some of the findings reported by Soviet investigators; it includes information presented during joint Working Group meetings with U.S. investigators.

Table 1. Summary of Cardiovascular Observations During Skylab Missions*

Cardiovascular deconditioning was observed during flight; changes appeared to be adaptive in nature and tended to stabilize after 4 to 6 weeks.
Cardiovascular changes did not impair crew health or ability to function effectively in weightless flight.
Inflight lower body negative pressure tests provided a fairly reliable predictive index of postflight cardiovascular status.
Inflight cardiac electrical activity as measured by vectorcardiogram was not significantly altered and remained within physiological limits.
Decreased cardiac output noted in crewmen postflight; thought to be related to reduced blood volume.
Single episode of significant cardiac arrhythmia noted in one Skylab 2 crewman during exercise early in mission.
No significant decrement in work capacity or physiologic responses to exercise during flight.
All crewmen exhibited decrease in work capacity and altered physiologic responses to exercise after flight including a decrease in maximal oxygen uptake.
Skylab 3 and 4 crews returned to preflight cardiovascular status by the fourth or fifth day and the Skylab 2 crew recovered on the 21st day postflight. Increased exercise by Skylab 3 and 4 crewmen during flight thought to be a factor in improved recovery rate.

* Modified from Dietlein, 1977.

Table 2. Cardiovascular Effects of Long Soviet Space Missions (96-185 days)*

Increased values inflight

Heart rates moderately greater than preflight values

Ejection times (transient)

Stroke volume and cardiac output, first 2 to 3 weeks inflight

Cerebral blood flow†, first 3 to 4 months; then return to preflight values in some, but not all, cosmonauts

Jugular vein pressure

Decreased values inflight

Peripheral resistance

Systolic arterial blood pressure

Venous pressure in legs, average drop 17 mm Hg

Leg volume

Postflight manifestations

Fatigue
Dizziness
Sensation of increased body weight
Tachycardia
Decreased stroke volume and ejection time
Orthostatic intolerance
Impaired locomotion and coordination
Reduced exercise capacity

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* Sources: (1) Soffen and Gazenko, 1981; (2) Gazenko et al., 1981; (3) Genin and Egorov, 1981.

† Estimated from rheographic measurements.

B. CARDIOVASCULAR RESPONSES TO WEIGHTLESSNESS AND SIMULATED WEIGHTLESSNESS

The marked physiologic changes in the cardiovascular system that occur as the body adapts to weightlessness and its ground-based analogues have been described in special NASA reports and the open literature (Bergman et al., 1976; Berry, 1970, 1974; Berry et al., 1966; Gazenko et al., 1981; Johnson et al., 1973, 1976; Johnston and Dietlein, 1977; Johnston et al., 1975; Nicogossian et al., 1976; Rummel et al., 1976; Sandler, 1980). For many cogent reasons, it has not been possible to conduct exhaustive investigations of cardiovascular physiology in humans during space missions, especially in the first few critical hours and days. Therefore, to supplement data from space missions, emphasis has been placed on the use of ground-based models of weightlessness, an approach that permits flexibility in design and control of experiments (Nixon et al., 1979; Sandler, 1980).

Studies on experimental animals in space have not added significantly to the understanding of cardiovascular deconditioning. However, some limited but useful data were acquired from dogs (USSR) and from monkeys and chimpanzees (USA) prior to human spaceflight, and studies of animals in space may ultimately prove to be the only feasible means of acquiring certain types of data on cardiovascular deconditioning and other biomedical problems of spaceflight (Sandler, 1980).

Cardiovascular responses to weightlessness

Immediately after entering orbital flight, the body begins to adapt to the weightless environment. There is a shift of possibly as much as 2 liters of blood and interstitial fluid from the lower to the upper half of the body, with the major portion of the shifted volume entering the intrathoracic organs, including the heart chambers and pulmonary vessels. Soviet scientists have reported a sustained increase in jugular venous pressure (Yegorov, 1981). In the lower extremities, they observed a reduction of venous pressure and, by mission days 10-11, an average volume decline of 10%. Astronauts notice fullness in the head, stuffy noses, nasal voices, and slender legs, which they have termed "puffy faces and birdlegs" (Johnston and Dietlein, 1974, 1977; Money, 1981).

Mean resting inflight values of heart rate and of the arterial systolic and pulse pressures tend to be greater while arterial diastolic pressures tend to be less than the preflight values (Sandler, 1980). It is postulated, but not documented in flight, that the large, headward shift of blood volume rapidly induces a diuresis in response to increased right atrial pressure. In turn, this leads to a reduction in plasma volume (Lamb, 1966), which has been described as an actual and a functional hypovolemia, as reflected by postflight orthostatic intolerance and impaired

exercise capacity (Blomqvist and Stone, 1983). A negative fluid balance with a reduction in plasma volume may also result from decreased fluid intake during the initial hours or days of a space mission. Grigoriev (1981) emphasized that the question of diuresis early in orbital flight will remain uncertain until it is measured directly.

With few exceptions, electrocardiographic changes observed during space flight have been unremarkable (Dietlein, 1977; Genin and Egorov, 1981; Sandler, 1980; Smith et al., 1977) and were judged to be within normal physiologic limits (Dietlein, 1977). Skylab data showed increases in the magnitude of the maximum QRS and T vectors and an increase in the PR interval (Smith et al., 1977). Sporadic ventricular ectopy occurred during the Skylab missions. Slight but significant increases in the amplitudes of T and U waves have been reported in bed-rested subjects after 2 to 3 weeks (Sandler, 1980).

The average loss of weight in nine astronauts during the three manned Skylab missions was approximately 3 kg (Thornton and Ord, 1976). Factors that are presumably responsible for the loss of weight include negative fluid balance in response to fluid shifts and/or inadequate intake, skeletal muscle atrophy, and loss of body fat as a result of restricted caloric intake (Leach et al., 1979). Nixon et al. (1979) estimated that about one-half the loss of weight occurs within 3 days of the start of the mission and most probably results from a loss of interstitial fluid.

Yegorov (1981) reported the following responses to LBNP in cosmonauts during long-term missions: heart rate, peripheral vascular resistance, and the arterial pulse wave velocity increased, while stroke volume and cardiac output fell. The increase in calf volume in response to LBNP during flight was greater than the analogous response to simulated weightlessness.

After return to Earth, all astronauts and cosmonauts have exhibited some degree of cardiovascular deconditioning, regardless of mission length. It is characterized by inappropriate heart rate and blood pressure responses to the upright posture, head-up tilting, or LBNP. The responses include tachycardia, a drop in systolic blood pressure, and narrowing of pulse pressure. Fatigue, presyncopal signs and symptoms, and reduced exercise tolerance have been documented, as well as impaired locomotion. These manifestations of the altered state of the cardiovascular system and its controls have persisted for a few days to approximately 1 month postflight; however, the usual duration has been from 2 to 4 days. Echocardiographic measurements of cosmonauts after long space missions show a mean 25% decrease in left ventricular volume (Sandler, 1982a); however, there is no firm evidence of an actual loss of cardiac muscle.

Figures 1 and 2 are conceptual diagrams of the responses of the cardiovascular and related systems to weightlessness or its ground-based analogues.

Cardiovascular responses to simulated weightlessness

The effects of bed rest and other ground-based technics of simulating weightlessness are very similar to those outlined above for actual weightlessness. Despite universal acknowledgment that the ground-based models cannot be equated to the zero-gravity environment, they do approximate certain features of weightlessness and do permit controlled biomedical studies and tests of possible countermeasures (Nixon et al., 1979; Sandler, 1980).

Important differences in responses to ground-based models and the actual zero-G environment occur because the effects of gravity on the spatial distribution of pulmonary blood and gas volumes and flows cannot be avoided by either bed rest or water immersion: (1) the lungs are anatomically fragile; (2) the pulmonary vascular bed is the most compliant segment of the vascular system; and (3) because of the large differences between the specific gravity of the respiratory gases and the blood and tissues surrounding the alveoli and airways, pulmonary function is highly susceptible to changes in the direction and magnitude of the gravitoinertial force environment (Wood et al., 1963a). In addition, while the bed rest model reduces dependent systemic venous pooling, it cannot entirely eliminate it.*

Blomqvist and Stone (1983) note that a marked change in the hydrostatic conditions that prevail in man in the upright position on Earth results when subjects are exposed either to experimental bed rest, to head-out immersion in water, or to actual weightlessness. A redistribution of intravascular and interstitial fluid from the lower to the upper half of the body is the main, acute, hemodynamic effect. The mechanisms for adaptation to the relocated fluids and altered intravascular pressures associated with bed rest, immersion, or zero-G are thought to be basically similar. Hypovolemia, reduced stroke volume and cardiac output, orthostatic intolerance, and decreased exercise capacity are the common results of exposure to real and simulated weightlessness (Blomqvist and Stone, 1983).*

The various physiologic mechanisms respond more rapidly to head-out immersion than to bed rest. Nevertheless, bed rest has been used more extensively to simulate weightlessness because of its relative simplicity and freedom from immersion-induced

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* One member of the ad hoc Working Group suggested that the third and fourth paragraphs require altered emphasis (see Appendix, p.63-66).

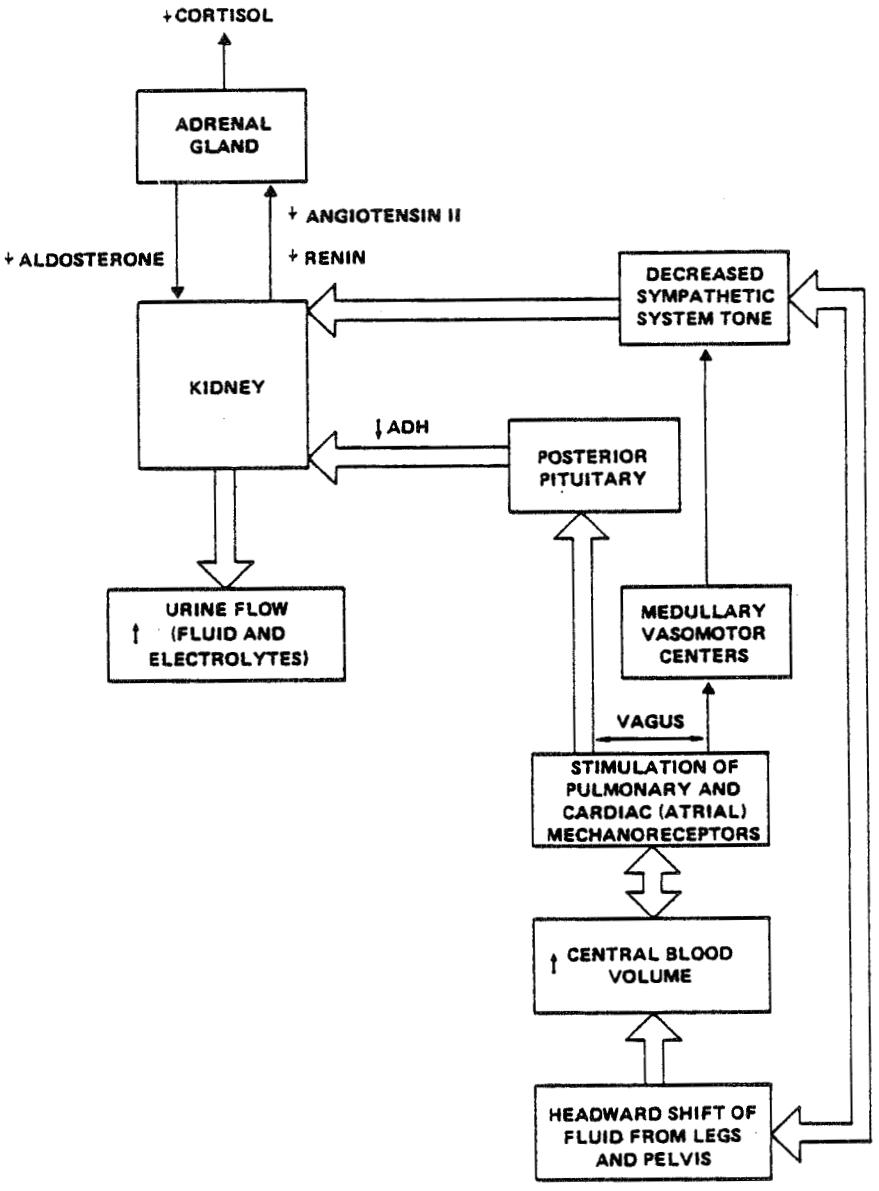

Figure 1. Circulatory events accompanying a change in posture (standing to lying) and possibly weightlessness (Sandler, 1980, with permission).

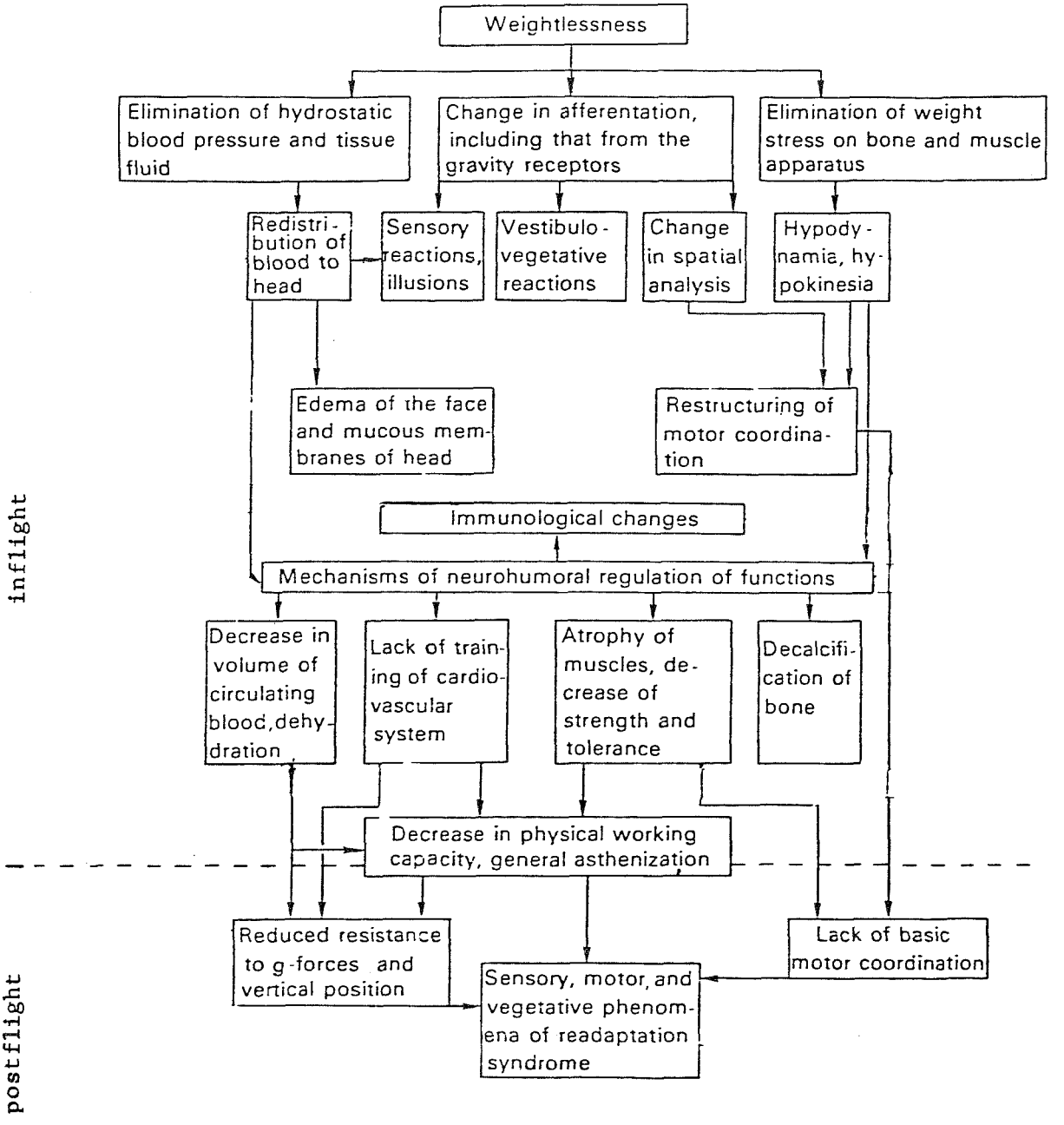
Weightlessness
Elimination of hydrostatic blood pressure and tissue fluid
Change in afferentation, including that from the gravity receptors
Elimination of weight stress on bone and muscle apparatus
Redistri-bution of blood to head
Sensory reactions, illusions
Vestibulo-vegetative reactions
Change in spatial analysis
Hypody-namia, hy-pokinesia
Edema of the face and mucous mem-branes of head
Restructuring of motor coordina-tion
Immunological changes
Mechanisms of neurohumoral regulation of functions
Decrease in volume of circulating blood, dehy-dration
Lack of train-ing of cardio-vascular system
Atrophy of muscles, de-crease of strength and tolerance
Decalcifi-cation of bone
Decrease in physical working capacity, general asthenization
Reduced resistance to g-forces and vertical position
Lack of basic motor coordination
Sensory, motor, and vegetative phenom-ena of readaptation syndrome
inflight
postflight

Figure 2. Pathogenesis of problems caused by the influence of weightlessness (modified from Genin and Pestov, 1971).

hydrostatic forces. Such forces act on the body to create a state of negative pressure breathing and, in turn, a shift of blood into the intrathoracic circulation (Sandler, 1980). Recent studies suggest that a head-down tilt of about 5° simulates the agravic qualities of weightlessness more closely than the supine position (Kakurin et al., 1976; Nixon et al., 1979). However, not all investigators concur in this conclusion (Hyatt and West, 1976).

Most cardiovascular responses to real and simulated weightlessness appear to be similar. However, some significant differences have been observed or postulated, such as the volume response of the lower extremities during LBNP. The extraordinary inflight pooling of blood in the legs induced by LBNP has been documented in the Skylab missions (Johnson et al., 1977) but it has not occurred in most bed rest studies of the changes in leg volumes during LBNP. However, interpretation of this difference should take into account the effect of differences in instrumentation used inflight versus that used in the ground-based studies. Also, a dramatic reduction of lower limb girth develops during space flight. Nixon et al. (1979) studied the cardiovascular changes in normal human subjects that occur during the first 24 hours of 5° head-down tilt bed rest. They recorded a mean total reduction of 0.9 liters in the volume of both legs, which, according to the authors, closely matches the initial, rapid phase changes observed during the Skylab studies.

Subjects experience a marked natriuresis and water diuresis during the initial hours of water immersion to the neck and during the first day or two of bed rest (Epstein, 1978). In addition, a kaliuresis of shorter duration than the natriuresis occurs in water immersion. Whether these changes occur in weightlessness is not known, but they have been postulated (Berry, 1973).

As a possible countermeasure against cardiovascular deconditioning, exercise has generally failed to prevent the orthostatic intolerance that results from simulated or actual weightlessness. However, postflight recovery time of the crews of Skylab missions 3 and 4 (4-5 days) was significantly less than that of Skylab 2 (21 days). The use of vigorous exercise by the crews of Skylab 3 and 4 may have accounted for the difference (Dietlein, 1977).

While certain evidence suggests that central venous pressure (CVP) in human subjects remains elevated throughout long space missions (Yegorov, 1981), results of bed rest studies suggest either that CVP does not change or that it increases transiently. After initiation of 5° head-down tilt, CVP in human subjects increased within 30 minutes to peak values and returned to near control values within 90 minutes (Nixon et al., 1979). However, in studies of human volunteers with indwelling venous catheters, there was no increase in CVP during 7 days of 5° head-down tilt (Katkov, 1981). The anatomical zero reference point for measuring central venous pressures is treated on page 27.

Tables 3 and 4 list the generally recognized, prominent cardiovascular and other physiologic changes that have been reported from spaceflight and simulation studies. They include known and postulated mechanisms, and identify associated unanswered questions and problems. Firmly established mechanisms for the listed responses either do not exist or fall short of providing complete explanation. This lack of definitive information results in a relatively large listing of hypotheses and concepts, many of which are under investigation.

C. COUNTERMEASURES

Attempts to prevent or control cardiovascular deconditioning have involved inflight, reentry, and postflight measures. Also, various interventions have been tested during and after bed rest and other ground-based analogues of weightlessness. These measures have included inflight exercises and LBNP, venous occlusion, pre-reentry fluid and electrolyte replacement, use of anti-G suits during and following reentry, and postflight supportive measures (Sandler, 1980). In addition, drugs and hormones have been tested experimentally. Among the more promising countermeasures that have been evaluated in manned space flight are active exercise, hydrostatic stressing of the lower half of the body by repetitive LBNP, oral fluid and electrolyte replacement before reentry, and the use of anti-G posture and anti-G suits during reentry (Johnston and Dietlein, 1977; Sandler, 1980; Yegorov, 1981).

Artificial gravity used during the flight of the Kosmos 936 biosatellite appeared to protect rats against certain musculoskeletal degenerative effects (Oganov, 1981; Simmons, 1981). Available evidence from these and other biosatellite experiments is insufficient to establish whether degenerative effects occur in the rat myocardium during zero-G exposures of approximately 3 weeks. No gross or histologic (by light microscopy) abnormalities of the myocardia of such animals have been detected (Gazenko et al., 1980). However, myocardial phosphorylases a and b were increased postflight, and a mean reduction of 44% in myosin ATPase activity was found. Baransky et al. (1980) reported changes in the structure of mitochondria, smooth endoplasmic reticulum, and glycogen content of cardiac muscle cells of rats exposed either to zero-G or to 1.0 G produced by an onboard centrifuge during the 21-day flight of Kosmos 936. Thus, artificial gravity did not prevent the observed ultrastructural changes.

Expert opinion is divided about the extent of protection offered by such measures as vigorous, regularly scheduled exercise, repeated LBNP, and pre-reentry fluid and electrolyte replacement (Dietlein, 1977; Sandler, 1980; Thornton, 1981; Yegorov, 1981). From their experience with long-term manned flights, Soviet investigators are sufficiently convinced of the efficacy of such measures

Table 3. Mechanisms of Human Cardiovascular Adaptation to Real or Simulated Weightlessness

	Observed Responses*	Known Mechanisms	Postulated Mechanisms	Essential Missing Information
1.	Rapid shift of intravascular and interstitial fluid to upper half of body	Absence of all hydrostatic (gravitational) pressure gradients	Altered vascular compliance and/or capacity; altered cardiac output and distribution of blood flow; hormonal and renal changes in chronic adaptation	Acute and chronic effects on: right atrial pressures; pulmonary blood and gas volumes and flows; left atrial pressures; shapes and pressure-volume dynamics of cardiac chambers; shape and position of diaphragm; splanchnic and cerebral blood volumes, pressures, and flow distribution; pressure and volume receptors.
2.	Echocardiographic evidence of a mean 25% decrease in left ventricular volume after long missions	Hypovolemia	Reduced peripheral resistance, diastolic and arterial blood pressure; net decrease in cardiac workload	Whether any loss of myocardial mass occurs
3.	Diuresis and natriuresis during initial 24-48 h	Suppression of ADH release via stimulation of atrial pressure receptors (immersion; bed rest)	Gauer-Henry reflex in weightlessness? Changes in pressure and neurohumoral content of cerebrospinal fluid (CSF)?	Whether diuresis and natriuresis occur in first 24-48 h of 0-G: whether physiologically significant changes in CSF pressure and neurohumoral content occur; effects on ADH and aldosterone
4.	Hypovolemia of 300-500 ml develops within 24-48 h	Diuresis and increased transcapillary fluid shift from lower body tissue space	Headward fluid shift activates volume or low-pressure receptors; inactivity; imbalance of fluid intake and output	Whether hypovolemia occurs independently of volume or low-pressure receptor function. Whether mental stress early in mission affects fluid shift and diuretic mechanisms via sympatho-renal or other neuroendocrine pathway; right atrial pressures; pulmonary blood flow and volume; left atrial pressures; position, shape, and pressure-volume dynamics of cardiac chambers; cardiac output and magnitude of sympathetic activity; systemic vascular resistance.
5.	Relative to preflight values, Skylab inflight mean resting heart rates, systolic, and pulse pressures increased; diastolic and mean arterial pressures decreased	Stimulation of volume and low-pressure receptors by relative hypervolemia in upper half of body	A widened pulse pressure with an increased heart rate suggests an increased cardiac output and reduced peripheral resistance	Status of cardiovascular reflexes in real and simulated weightlessness

* The most frequently, but not invariably, reported human adaptive responses to real or simulated weightlessness. Postflight and post-simulation effects are listed in Table 4.

Table 3. (continued)

Observed Responses	Known Mechanisms	Postulated Mechanisms	Essential Missing Information
6. Increased left ventricular end-diastolic and end-systolic volume in first 24 h of 5° head-down tilt; stroke volume and cardiac output unchanged	Increased EDV with unchanged stroke volume suggests larger ESV	Reduced contractility of heart, but increased systolic blood pressure also suggests an increased after load	Accurate, more complete data
7. Reference baseline values, decreased LVED volume and stroke volume with unchanged or reduced cardiac output after 2 wk bed rest; more pronounced in females	Hypovolemia and lower arterial pressure load coupled with tachycardia	Increased ejection fraction and relative tachycardia offset decreased LVED volume	Inconsistencies in results by different investigators should be resolved; more accurate and more complete data
8. Soviets report increased stroke volume and cardiac output, peak values at 6-9 d of head-down tilt and first 2-3 wk inflight	Increased filling pressure from headward shift of body fluids; Starling's mechanism via greater filling of heart ventricles	Reduced peripheral vascular resistance resulting in decreased cardiac workload	Same as in item #1, including end-diastolic and end-systolic volumes; accurate cardiac output and vascular pressure data
9. Soviets found decreased inflight peripheral vascular resistance and arterial blood pressure	Increased stimuli to low-pressure mechanoreceptors; increased pulse pressure causes greater discharge of high-pressure receptors	Stimulation of mechanoreceptors as a result of altered intravascular pressures; altered peripheral sympathetic function; impaired norepinephrine release	Same as in item #8; distribution of change in vascular resistance in different body regions
10. Transient elevation (+2.7 cm H_2O) central venous pressure in 5° head-down tilt (total duration of effect 90 min); recent USSR data do not confirm	Cephalad shift in circulating blood volume and extracellular fluids; natriuresis and diuresis	Reduced plasma volume; stress relaxation (or creep) of the capacity vessels	Same as in item #1; accurate data on CVP mandatory for understanding mechanisms of cardiovascular adaptation; variance in data needs resolution
11. Soviets report sustained increase in jugular vein pressure inflight; also elevated cerebral blood flow first 3-4 mo inflight estimated by rheography	Hemodynamic effect of cephalad shift of body fluids; absence of vertical gradient in vascular pressures at zero-G	Inactivity; relative disuse of lower extremities; loss of muscle pump	Same as in item #1; gradual trend to normal cerebral flow in some cosmonauts needs confirmation; whether CVP is chronically elevated; complete picture of redistributed blood flow and effects thereof

Table 3. (continued)

	Observed Responses	Known Mechanisms	Postulated Mechanisms	Essential Missing Information
12.	Relative to inflight resting values, inflight lower body negative pressure (LBNP) tests showed <u>increases</u> in: heart rate, peripheral resistance, mean arterial pressure, diastolic pressure, pulse wave propagation, and blood pooling in legs*; and <u>decreases</u> in systolic and pulse pressures, stroke volume and cardiac output	Reflex C-V responses to reduced blood volume; interstitial fluid in legs decreased; lower vascular tone; impaired venous return including muscle pump	Reduced arterial mechanoreceptor activity; increased vasomotor center activity; enhanced adrenergic activity; decreased responsiveness of vascular smooth muscle to adrenergic neural activity; altered venous capacitance and/or capacity; decreased skeletal muscle tone; large displacement of blood to lower half of body relative to Earth conditions; increased distensibility of lower limb veins	More accurate and complete information is needed; confirmation of inflight vs preflight LBNP data; sympathetic activity; systemic vascular capacity; accurate data on magnitude of fluid volume change trapped in lower body during LBNP; status of high- and low-pressure cardiovascular reflex systems; explanation for apparent paradox of decreased peripheral vascular receptor activity during increased arterial blood pressure
13.	Altered vascular compliance and capacity in such responses as high degree of blood pooling in legs during inflight LBNP		Passive stretch and/or increased distensibility of veins; altered peripheral sympathetic function; reduced vascular tone, transmural pressure; collapsed veins	Does weightlessness induce transient or sustained changes in vascular compliance and capacity, atrophy of vascular musculature, vascular remodeling? Distinct roles of high- and low-pressure receptor reflexes? Separate information on vessels in upper and lower halves of the body
14.	Decreased red blood cell mass proportional to hypovolemia		Changes in erythrocyte shape? Reduced release of erythropoietin associated with reduced hemoglobin concentrations and oxygen delivery to the kidney?	Is this effect fully reversible in long-term flights? Is loss independent of 0-G? Relationship between loss and observed changes in red cell shape? What is basic mechanism?
15.	Near 10% decreased inflight vital capacity, Skylab 3 pilot and all crew of Skylab 4		Cephalad shift of diaphragm? Redistribution of body fluids to thorax? Direct result of 5 psia cabin pressure?	The practical significance of the observed changes; magnitudes and spatial distribution of pulmonary blood and gas volumes and flows; shape and position of diaphragm
16.	Decreased urinary norepinephrine excretion in bed rest studies; however not all studies confirm		Changed functional state of sympathetic nervous system? Impaired norepinephrine release or uptake into granules?	Control mechanisms; resolution of inconsistencies in research results; effect of tension (mental stress) on this phenomenon

* Relative to preflight values

Table 3. (continued)

	Observed Responses	Known Mechanisms	Postulated Mechanisms	Essential Missing Information
17.	Skylab inflight hormones: plasma cortisol, angiotensin I increased or normal; plasma ACTH, insulin, aldosterone decreased; urinary cortisol, aldosterone, total 17-KS increased; trend toward decreased urinary ADH, epinephrine and norepinephrine		Increased intracranial pressure alters control and production of CNS regulatory hormones; cephalad shift of blood and interstitial fluid causes multiple hemodynamic changes that influence homeostasis of water and electrolyte metabolism	Resolve apparent paradox of increased sodium excretion in presence of high plasma aldosterone; confirm head-down bed rest as model of O-G for study of hormone and electrolyte responses; assess relative influence of O-G vs other environmental and operational factors
18.	Skylab inflight electrolytes: plasma sodium decreased; urinary sodium increased; trend toward increased plasma potassium; urinary potassium increased		Increased cardiac output or some endocrine change acting on the kidney	Confirm increased plasma potassium and increased urinary potassium excretion; source of these changes in potassium turnover; extend knowledge of endocrine changes

Table 4. Mechanisms of Postflight and Post-simulation Orthostatic Intolerance

	Observed Responses*	Known Mechanisms	Postulated Mechanisms	Essential Missing Information
1.	Tachycardia with body upright or with head-up passive tilt; postural hypotension, sometimes with presyncope or syncope: LBNP tolerance reduced post-flight and after simulation	Hypovolemia; decreased stroke volume	Loss of vascular and muscular tone, especially lower extremities; abnormal reflex cardiovascular regulation; increased distensibility of leg veins; decreased tissue pressure in lower extremities; reduced baroreceptor sensitivity; increased vagal discharge plus existing sympathetic response to upright tilt or standing; decreased cardiac work capacity; impaired release of endogenous norepinephrine	Nature and extent of deterioration of reflex mechanisms responsible for cardiovascular function; why is degree of C-V dysfunction greater than expected from amount of hypovolemia? Effect of O-G on (1) sensitivity, numbers, distribution of C-V mechanoreceptors, (2) thermoregulation; (3) right atrial pressure; (4) pulmonary blood and gas pressures and flows; (5) left atrial pressure; (6) functional dynamics of cardiac chambers
2.	Marked reduction in maximal and submaximal work capacity, upright and supine	Decreased stroke volume	Decreased oxygen uptake, ventilatory volume, maximal heart rate, LVED volume, and cardiac filling pressures and output; physical inactivity; reduced muscle strength, tone, blood pumping action; decreased heart size and cardiac work capacity	Nature and extent of effects on reflex mechanisms that control cardiopulmonary function; effects on C-V mechanoreceptors; functional dynamics of cardiac chambers; effect of exercise inflight and during simulation
3.	No increase in pooling of blood in legs of most bed-rested subjects during LBNP tests; marked increase inflight		Difference in responses suggests a a factor in ground-based models that sustains vascular and skeletal muscle "tone"; most likely the hydrostatic pressure gradients of gravity. Periodic turning of subject from prone to supine also probably affects results.	Same as in #1 above
4.	Tolerance for acceleration of +2.5G_z (eyeballs down) declined in 20% of centrifuge-experienced subjects after 24 h bed rest; tolerance less for inexperienced subjects		Hypovolemia and decreased interstitial pressure in lower extremities	Same as in #2 above

* The most frequently reported responses; however, some results are inconsistent with the responses listed above.

that they would consider their omission during long-term missions as unethical (Soffen and Gazenko, 1981; Yegorov, 1981). NASA scientists tentatively concluded that, compared with the results of Skylab 2, the relatively superior pattern of postflight cardiovascular readaptation of the crews of Skylabs 3 and 4 probably resulted from the vigorous exercise program during the latter two missions (Dietlein, 1977). However, lack of reliability, incomplete protection or impracticality for space flight use have caused some investigators to regard such countermeasures as marginally effective or ineffective in preventing cardiovascular deconditioning, particularly the orthostatic intolerance, associated with weightlessness and its ground-based models (Johnson et al., 1977; Sandler, 1980).

Another approach to the subject of countermeasures involves the apparent resistance of some space flyers to cardiovascular deconditioning as measured by the time required postflight to return to preflight physiologic status. It may be possible to correlate certain physiologic or behavioral characteristics of such individuals with their partial resistance to cardiovascular deconditioning.

In spite of variable and sometimes contradictory results obtained during studies of countermeasures, certain approaches have appeared promising enough to warrant further research and development. Among these inflight countermeasures are dynamic exercise, static exercise (Stremel et al., 1976), centrifugation (Kotovskaya et al., 1980; Shulzhenko et al., 1976; White et al., 1966), prolonged LBNP stressing (4 h/d) combined with oral replacement of fluids (Hyatt and West, 1977), and the use of anti-G suits or leotards (Berry, 1975; Buyanov et al., 1967; Hordinsky, 1977; McCally et al., 1968).

D. RELATED FACTORS AND PHYSIOLOGIC FUNCTIONS

Reports of numerous investigations have suggested that the mechanisms of response of the cardiovascular system to weightlessness are multiple and not necessarily restricted to the attendant major fluid shift from the lower to the upper half of the body. In addition to weightlessness, other characteristics of the spaceflight environment should probably be taken into account such as the behavioral and physiologic effects of confinement, isolation, apprehension, monotony, and reduction in social contacts (Kozerenko et al., 1981).

Exposure to weightlessness influences fluid and electrolyte balance, metabolism of minerals and other nutrients, and certain endocrine functions. Thus, many variables are involved in assessing cardiovascular changes during complex interactions among the diverse organ systems and functions of the weightless body

(Pestov and Geratewohl, 1975). Consequently, it would be appropriate to conduct further studies of the sequence and interdependence of changes in cardiovascular, renal, endocrine, and sensory functions associated with weightlessness or its ground-based analogues (Bjürstedt, 1980; Whedon, 1978).

Table 5 lists responses that have been noted in physiologic systems and functions other than the cardiovascular system, per se. Whether these observed phenomena have a direct relationship to cardiovascular deconditioning is not established. The NASA research programs on fluid and electrolyte metabolism, renal function, musculoskeletal integrity, and vestibular function are aimed at resolving problems in these specific areas. Clearly, advances in understanding these responses may also extend knowledge about their relationships to cardiovascular deconditioning.

Table 5. Non-Cardiovascular Responses of Organs, Organ Systems, and Physiologic Functions Associated with Spaceflight or Ground-Based Simulation*

Vestibular disturbances and space motion sickness
Loss of red cell mass
Weight loss (probably from combination of metabolic, body fluid, and muscle mass losses)
Moderate loss of skeletal muscle mass
Moderate losses of calcium (skeletal) and phosphorus and nitrogen (skeletal muscle)
Inflight decreases in ADH secretion (except Skylab 2)
Inflight increases in aldosterone and cortisol secretion
Inflight increases in urinary excretion of sodium and potassium
Unimpaired renal function; elevated renal blood flow in bed rest
Reduced postflight exercise tolerance which may reflect musculoskeletal, hormonal, and nervous system changes as well as changes in the cardiovascular system; for example:
Possible change in the functional state of the peripheral sympathetic nervous system in terms of vascular resistance and venous tone; possible impairment of norepinephrine release or uptake into granules

* Sources: Dietlein, 1977; Sandler, 1980; Soffen and Gazenko, 1981.

IV. NASA'S PROGRAM OF GROUND-BASED RESEARCH IN CARDIOVASCULAR DECONDITIONING

The ad hoc Working Group examined the current NASA program of ground-based research in cardiovascular deconditioning to form an opinion of its potential to meet NASA's needs. The main sources of information were the NASA Research and Technology Objectives and Plans (RTOPs) and Research and Technology Resumes (RTRs) for Fiscal Year 1983, information presented by NASA scientists during the meeting of the ad hoc Working Group on July 6-7, 1982, and both published and unpublished information on the cardiovascular effects of space flight and its ground-based analogues.

In general, the RTOPs for the cardiovascular deconditioning program appear adequate in scope and content. The stated objectives for elucidation of the mechanisms of cardiovascular deconditioning are well conceived and scientifically sound. The current NASA program supports some degree of effort in most of the research recommended in the reports of the Space Science Board Committee on Space Biology and Medicine (Bricker, 1979) and the NASA Life Sciences Advisory Committee report of 1978 (Whedon, 1978).

The extant and planned research tasks documented for FY 1983 were compared with the Technical Objectives. Of the 17 tasks formally documented in the RTRs, 11 are devoted mainly to investigations of the underlying mechanisms of cardiovascular deconditioning; one to development and test of countermeasures, and five to development, test, and acquisition of improved methodology, equipment, and facilities. In connection with its basic research on cardiovascular deconditioning, the Ames Research Center (ARC) program includes a small amount of countermeasures testing with rhesus monkeys (anti-G suits; abdominal pressure) as well as some equipment and methodology development.

The ad hoc Working Group is aware of the practical difficulty faced by temporary scientific advisory bodies of quickly obtaining a complete picture of extensive research and development programs. Moreover, it recognizes that the NASA research program in cardiovascular deconditioning is dynamic, because the tasks are adjusted periodically as new research is begun and other tasks are completed. In addition, the ad hoc Working Group realizes that the program is somewhat hindered by fiscal limitations and by lack of awareness of and interest in NASA's biomedical problems by a large part of the potentially-participating scientific community. These considerations notwithstanding, the Working Group regards the program as generally appropriate, but perhaps not adequate in terms of the level of effort needed to meet the objectives listed in the RTOPs. The total number of research groups working on cardiovascular deconditioning is such that it will probably take many years to reach satisfactory solutions, particularly in working out those essential mechanisms that may lead to sound methods of intervention.

The difficulties of forecasting breakthroughs in basic research on the complex mechanisms of cardiovascular deconditioning make it infeasible to estimate a realistic schedule for resolution of key problems. Thus, the time for acquisition of necessary data on basic mechanisms is long-term, or probably more than 5 years. However, it is feasible to predict schedules of progress in such applied areas as improved countermeasures, improved test methodology, and associated equipment and facilities. The long-term nature of the basic research program may be acceptable to NASA planners in view of the absence of any identified, permanent, incapacitating cardiovascular effects of manned space missions to date.

The NASA research program reflects the current state-of-the-art. However, the state must be improved considerably. As is indicated in Section V, advances are needed in the precise understanding of the characteristics and mechanisms of cardiovascular responses such as: (1) the changes in right atrial pressure associated with cephalad blood volume shifts, (2) the magnitudes and spatial distributions of pulmonary blood and gas volumes and flows, (3) the associated changes in left atrial pressures, (4) position, shape, and pressure-volume dynamics of the cardiac chambers, (5) possible subacute and chronic changes in myocardial mass, (6) shape and position of the diaphragm and associated lung volumes, (7) magnitudes and spatial distributions of splanchnic and cerebral blood volumes and flows, (8) possible effects on (a) circulatory pressure and volume receptors, and (b) venous "tone" and capacitance, and (9) possible histopathologic and biochemical changes in the myocardium after exposures to real or simulated weightlessness. Equally important will be the development and verification of better ground-based models for simulating the flight environment of the astronauts and the development of more effective and practical countermeasures.

Inasmuch as an accurate understanding of underlying biologic mechanisms of cardiovascular deconditioning is ultimately essential to practical advances in spacecrew protection and welfare, and in view of the long-term nature of such investigations, it is not surprising that the research suggested by the ad hoc Working Group in this report resembles in many respects that of previous advisory groups.

V. OBSERVATIONS OF THE AD HOC WORKING GROUP ON CARDIOVASCULAR DECONDITIONING

Among NASA's dominant current and future goals are the productive operation of the Shuttle-based Space Transportation System, and the development of a manned space station in low Earth orbit (1980s). Evaluation of the biomedical research program in cardiovascular deconditioning should take into account a proper balance between basic and applied research in order to assure progress in the primary missions of the agency. Although the number of persons who have participated in space flights is limited, the absence of serious adverse biomedical effects is encouraging: no mission has been reported to have been compromised by biomedical events, and all observed biomedical effects appear reversible. Thus, space mission programmers feel reasonably confident about the ability of carefully selected and trained spacecrews to carry out orbital missions of at least 6 months' duration.

Nevertheless, significant questions arise concerning the human adaptability to and recovery from the effects of more prolonged missions and concerning the ability of certain future space flyers to cope with weightlessness and other factors in the spaceflight environment. For example, the scientists and technicians who will participate in the forthcoming missions of the Shuttle-Spacelab will not all be experienced test pilots who will meet the most stringent medical standards for flying. Instead, they will tend to be older and will more nearly represent the average population in terms of physical condition and prior aerospace experience (Sandler, 1981).

In view of uncertainties about human tolerance for more prolonged missions than heretofore, whether the adaptive changes in the cardiovascular system are truly reversible after more prolonged exposure, and whether "ordinary" human beings can adapt and function in such programs as Shuttle-Spacelab, a carefully drawn research program in cardiovascular deconditioning seems highly justified.

A. HEMODYNAMIC FACTORS

1. Current Status

It is an accepted fact that a cephalad shift of blood volume occurs at the onset of exposure to weightlessness. Most experts agree that this initial, major hemodynamic effect is probably responsible for the cardiovascular deconditioning which follows. Current views of the probable mechanisms involved in the cardiovascular deconditioning associated with space flight are summarized in Section III, in particular in Table 3.

Knowledge of the extent and nature of cardiovascular system changes during the first day or two of spaceflight is scanty, and only a few reports of such temporal data from simulation studies in human subjects have appeared (Blomqvist et al., 1980, 1981; Nixon et al., 1979). Information is incomplete about the regional anatomical and temporal aspects of redistribution of blood flow during weightlessness and about the significance of such redistribution on cardiovascular adaptation and deconditioning.

In this report, the terms venous compliance and venous capacitance are synonymous and are defined as representing the volume change per unit pressure change (Gow, 1980; Shoukas and Sagawa, 1971). Vascular capacity refers to the volume of blood contained in the capacitance vessels at a given pressure (Folkow and Neil, 1971).

The complex role of the veins in cardiovascular homeostasis has been reviewed by Shepherd and Vanhoutte (1975), Hainsworth and Linden (1979) and Rothe (1983). From animal studies, it appears that non-splanchnic venous activity is much less responsive to cardiovascular reflexes than are splanchnic venous responses (Brunner et al., 1981; Shepherd and Vanhoutte, 1975; Rothe, 1983). Furthermore, compensatory venous responses appear to be predominantly from changes in unstressed volume rather than from changes in compliance. Therefore, estimates of systemic vascular capacitance changes, based on studies of forearm or leg venous compliance in people, may be either grossly underestimated or misleading.

There is a limited understanding of the degree, temporal development, and duration of changes in pressure and composition of the cerebrospinal fluid (CSF) associated with weightlessness and its analogues. The operating point of the heart relative to the Frank-Starling mechanism is not well defined. Finally, although data from humans during spaceflight do not suggest a respiratory hazard or irreversible cardiac changes, information is insufficient to rule out potential pathologic consequences of altered cardiopulmonary pressures during prolonged exposure to zero-G.

2. Critical Questions

The Working Group raised the question about whether the heart or the vascular system is mainly responsible for the adaptive and "deconditioned" responses of the cardiovascular system. They discussed the related question concerning possible significant changes in venous compliance and capacity and the location, nature, extent, and dependence upon the cephalad shift of blood volume of such changes in the venous system. Another related

question was whether significant changes of intraabdominal pressure occur during weightlessness, and the possible influence of abdominal muscle tone on such pressures.

The participants considered whether disappearance of gravitational pressure gradients in the lungs during zero-G may play a role in the adaptive or deconditioning process, and whether such gradients may influence the adjustments of the cardiovascular system to prolonged bed rest. The hemodynamic significance of the absence of pressure gradients within the thorax may be of equivalent or even greater importance than is the absence of these gradients in the lower extremities. The thoracic blood volume considerably exceeds that in the legs, and the absence in the zero-G environment of the 15-20 cm vertical pressure gradients in the very compliant pulmonary vasculature, which are normally present at 1-G irrespective of body position, must have significant effects on the spatial distribution of pulmonary blood and gas volumes and flows and consequently on right and, particularly, left atrial filling pressures in the agravic environment.

A basic question that remains unanswered is whether the physical inactivity imposed by the limitations of the spacecraft is more or less important than the headward shift of blood and fluids in the genesis of the deconditioning response. Although some evidence suggests that a schedule of vigorous inflight exercises moderates the deconditioning, the issue is unclear. Two additional questions considered to be significant are: how close is the operating point of the astronaut's heart to the plateau of the Frank-Starling curve during various phases and activities of space flight, and what is known of the exact triggering mechanism that leads to syncope?

3. Suggested Research

It is necessary to assess cardiovascular function and autonomic control at various stages of actual or simulated weightlessness. Multiple endpoints of cardiovascular function should be measured, such as central venous pressures, heart rate, ECG, systolic and diastolic arterial pressures, cardiac output, pressure-volume dynamics of the cardiac chambers, the magnitudes and spatial distributions of pulmonary blood and gas volumes and flows. Vital capacity, residual lung volume, and pulmonary diffusing capacity should also be measured, as should intracardiac and vascular transmural pressures.

Very small (1-5 cm water) variations in right and left atrial pressures may be of considerable hemodynamic significance. The pathophysiologic significance of venous pressure values is difficult to evaluate unless the anatomic zero reference point for reported values is accurately specified. The midpoint of the dorsal-ventral dimension of the thorax measured at the junction of

the second intercostal space at the sternum is generally accepted as the mid-chest level and as a suitable reference point for measurement of circulatory pressures (Greenleaf et al., 1974).

Another useful endpoint for assessing cardiac fuction is the E-max approach of Suga and Sagawa for estimating contractility (Sagawa, 1981), if adequate estimates of ventricular pressures and volumes become available. This concept of E-max has been used experimentally by Nixon et al. (1982). With regard to the operating point of the heart relative to the Frank-Starling curve, an investigative approach might involve the measurement of cardiac output while the central venous pressure is raised or lowered by applying positive or negative pressure, respectively, to the lower half of the body by means of the lower body plethysmograph.

A good approach to the analysis of vascular changes could be measurement of changes in venous pressure-volume relationships in a model of deconditioning. Measures of venous compliance do not necessarily reflect changes in the venous pressure-volume relationship because the compliance may be relatively constant while the unstressed volume is changing. Nevertheless, useful measurements might include serial changes in human forearm venous compliance by plethysmography, and serial changes in human venous "tone" induced by a standard LBNP protocol at selected stages of real or simulated space missions.

In animals, measurements may be made of changes in central venous pressure as a function of intravenous infusion of known volumes of fluid while holding cardiac output constant by means of the "Scher technic" (Bennett et al., 1982; Wyss et al., 1982). This last set of measurements would provide an estimate of changes in total systemic vascular compliance. If the cardiac output is constant, the central venous pressure reflects the changes in pressure in the systemic vascular capacitance vessels, and so systemic compliance may be estimated as: (change in blood volume)/(change in central venous pressure). There are no noninvasive technics yet available for measuring vascular capacitance. The mean circulatory pressure approach, e.g., Drees and Rothe (1974), might be used.

With respect to blood volume, the quantity and patterns of shifts of blood volume between the central (thoracic) compartment and the remainder of the cardiovascular system should be determined during representative phases of actual and simulated space flight. Provided a reliable method can be developed, absolute changes in venous volume of the limbs of bed-rested subjects should be measured with and without LBNP. An attempt should be made to improve plethysmographic technics to enable direct assessment of absolute volume changes, rather than percentage changes. Additional studies of human hemodynamic responses to head-down tilt should be done to expand the data base, to evaluate further the efficacy of this procedure as a model of weightlessness, and

to resolve apparent US/USSR differences in central venous pressure data (Katkov, 1981; Nixon et al., 1979).

For blood volume determination, the dye-dilution technic has proven reliable. Three good non-invasive methods for measuring cardiac output in human subjects are carbon dioxide, acetylene, or nitrous oxide rebreathing. Stroke volume measurements by 2-D echocardiography and nuclear cardiography are well established, but of limited precision. For more precise measurement of cardiopulmonary dimensions, heart chamber volumes, and myocardial mass in living subjects, more sophisticated imaging devices may be required. An example is the Dynamic Spatial Reconstructor (DSR) which has been developed at the Mayo Clinic (Ritman et al., 1980; Robb, 1982; Wood, 1978; Wood et al., 1982). This system provides high speed, synchronous, volumetric, scanning tomography. It may be feasible to develop a scaled-down version of the DSR which would be an affordable approach to dynamic imaging that transcends current methods.

Other valuable imaging methods for such studies include digital subtraction angiography, nuclear magnetic resonance (NMR), and computerized tomographic (CT) scanning. In animal studies, a promising approach to visualizing ventricular dynamics is biplanar cineventriculography of the heart, in vivo, with endocardial screw markers implanted via an intravenous catheter (Davis et al., 1980). Concerning the mechanism that triggers vasovagal syncope, evidence suggests that the response is related to diminished end-systolic volume of the heart. Therefore, measurements of changes in cardiac volume during provocative stressing should be helpful in such studies.

Finally, the role, if any, of alterations in the CSF pressure and composition in influencing cardiovascular responses should be identified.

Because of the possibility that 20 minute exposure to approximately 1.5 $+G_Z$ during reentry of the Shuttle Orbiter may interfere with astronaut performance, studies of the hemodynamic and possible associated central nervous system effects of approximately 20 minute exposures to 1.5-2.0 G_Z in seated healthy human subjects should be carried out before and after bed rest. The use of a photoelectric earpiece and associated circuitry for continuous simultaneous recordings of the blood content of the ear, the ear opacity pulse and arterial oxygen saturation for non-invasive monitoring of the subjects' hemodynamic status should be investigated (Wood et al., 1963 b,c) along with ultrasonic methods for detection of temporal artery flow (Sandler et al., 1977). Recordings of these parameters could be obtained in three types of exposures in random sequence: a control relaxed exposure, an exposure with a G-suit inflated to about 40 mm Hg, and an exposure with the G-suit inflated while pressure breathing at a moderate level of

about 20 mm Hg. It would be of considerable additional value to carry out these exposures when subjects are breathing either air or 100% oxygen. Chest roentgenograms should be made before and immediately after exposures to study the probable occurrence of dependent atelectasis during such exposures and associated pulmonary arteriovenous shunts for correlation with possible ear oximeter arterial saturation changes.

B. EFFECTS OF SPACE FLIGHT ON CARDIOVASCULAR SYSTEM RECEPTORS

1. Current Status

The mechanical, chemical, and neurohumoral receptors in the cardiovascular system probably have key roles in the biologic responses to zero-G including adaptation, orthostatic intolerance, and the deadaptation process. Precise knowledge of the effects of weightlessness on these receptors is fundamental to progress in elaborating the mechanisms of cardiovascular deconditioning. The responses to excitation of the low-pressure baroreceptors hold special interest. A possible defect in the reflex control of the circulation, induced by zero-G, is especially important during reentry from orbital flight and after return to the upright posture on Earth.

The ad hoc Group reiterated the concern of many investigators as to the possible role of cardiac "volume receptors" that may act through antidiuretic hormone (ADH) release from the pituitary to induce diuresis in response to increased thoracic blood volume--the Gauer-Henry reflex. With this proposed reflex, an increased blood volume (or headward shift of volume) distends the left atria and stimulates low pressure, volume receptors that have afferent endings in the brain. The system acts to reduce ADH secretion. This, in turn, leads to an increased urinary output of water to reduce the blood volume. Though the concept is attractive and has been rather extensively studied, Goetz et al., (1975) have raised doubts as to whether low pressure volume receptors indeed have an important influence on water handling by the kidney. Many of the technics used to increase atrial transmural pressure also influenced cardiac output. Further, the response appears to be transitory, and so, like the arterial baroreceptors, is probably of minor importance in long-term control of cardiovascular homeostasis. Nonetheless, the pulmonary venous and atrial receptors are probably influenced by the headward shift of fluid during weightlessness; therefore, reflex changes should be studied. Goetz and Bond (1971) reported that a reduced left atrial transmural pressure of 6-8 mm Hg caused a 2 mm Hg increase in central venous pressure. This suggests an influence of these atrial receptors on the capacitance system, but later studies with denervated atria (vagi and spinal afferents cut) showed similar renal responses and a decreased arterial pressure with reduced atrial transmural pressure (see ref., 92a in Goetz et al., 1975). The technological problems discussed by

Goetz et al. (1975) are formidable. The possible pitfalls must be carefully considered or else totally worthless data will be gathered at great expense and possible risk. For example, the excitement associated with entry into space may seriously modify or even reverse any diuretic response.

The highly significant changes in heart rate during LBNP stressing of spacecrews inflight or of bed-rested subjects do not necessarily imply that the cardiovascular system is "deconditioned," but such an exaggerated heart rate response appears to serve as a valuable index to the deconditioning process.

2. Critical Questions

A fundamental question is whether the atrial and ventricular receptors exert regulatory control of the heart and vessels and of the release of vasopressin and aldosterone during zero-G. An important associated problem is whether weightlessness induces changes in the number and sensitivity of the autonomic receptors of the cardiovascular system, including the α- and β-adrenergic receptors and the muscarinic receptors. Further, if exposure to weightlessness results in impairment of circulatory reflex control, is the defect that is responsible for postflight cardiovascular instability localized in the baroreceptors, the brainstem, the afferent or efferent limbs of the reflex arc, or in the effector cells themselves?

Increased cardiac filling pressure stimulates sensory receptors in the atria and ventricles, the former eliciting an increase, and the latter a decrease in heart rate. Does cardiac filling pressure increase under zero-G conditions and, if so, which of the foregoing effects prevails?

3. Suggested Research

The effects of real and simulated weightlessness on the numbers and sensitivities of the mechanical, chemical, and neurohumoral receptor sites in the cardiovascular system should be investigated in animal and human models of cardiovascular deconditioning. Progress in this area will depend heavily on advances in methodology and instrumentation.

It is important to locate precisely the site of the defect in the reflex control of the circulation that is responsible, at least in part, for the cardiovascular deconditioning. Procedures for assessing the functional changes in the reflex arcs activated by the baroreceptors of the cardiovascular system might include studies in large, non-human primates for: (a) measuring responses of the isolated carotid sinus to analyze the afferent limb, (b) examining the influence of surgical denervation of afferent and efferent pathways, (c) recording responses to sympathetic nerve

stimulation or to adrenergic agonists to analyze the efferent side, and (d) pharmacologic blockade and responses to such maneuvers as hand grip or a cold pressor test to evaluate the sympathetic component.

Research should be done to develop suitable methods for measuring baroreceptor function, per se, in conscious subjects. This should include assays in laboratory animals for possible changes in autonomic receptor density resulting from exposure to weightlessness and its ground-based analogues. Test animals must be large enough to exhibit hemodynamic responses that closely approximate human responses. Opportunities to investigate functional changes in baroreceptor reflexes are offered by studies of subjects undergoing bed rest and other ground-based models of weightlessness.

Lower body negative pressure, coupled with measurement of atrial and ventricular pressures, is a means of studying the role of atrial and ventricular mechanoreceptors in cardiovascular function. To distinguish between low- and high-pressure receptors, LBNP can be used to alter the activation of low-pressure cardiopulmonary receptors, and neck suction (Eckberg et al., 1975) can be used to alter the activation of the high-pressure carotid sinus receptors. The caveats and procedural guidance emphasized by Eckberg (1982) are applicable to tests of human autonomic function and should be considered in designing such experiments.

Past studies of histopathologic changes in the heart from infusions of catecholamines have not emphasized possible effects on adrenergic receptor sensitivity and density (Haft et al., 1972; Selye and Bajusz, 1959). In view of possible imbalances of sympathetic function and norepinephrine secretion during and after adaptation to zero-G, investigation of the effect of elevated and depressed levels of circulating catecholamines on adrenergic receptor density and sensitivity in the cardiovascular system appears to be warranted.

C. CATABOLIC, ATROPHIC, AND HISTOPATHOLOGIC CHANGES

1. Current Status

The possibility of degenerative changes in the cardiovascular system is a high-priority topic for resolution. Rats exposed to weightlessness in biosatellites for 18 to 21 days have not shown gross or histologic (light microscope) pathologic changes (Gazenko et al., 1980). However, immobilized, horizontally-casted monkeys and immobilized rabbits have shown histopathologic changes in the myocardium. Somewhat similar myocardial changes were observed in the hearts of three cosmonauts who experienced a fatal, premature decompression of their spacecraft during atmospheric reentry after

a 3-week mission; however, no published report of these findings was available to the ad hoc Group. Most human data from space flight and bed rest studies do not suggest any resultant myocardial pathology, although there is good echocardiographic evidence of diminished heart size of spacecrews after long-term missions.

2. Critical Questions

It is essential to know whether changes in the cardiac mass of astronauts result from exposure to zero-G. Similarly, the nature and extent of degenerative changes in the hearts of immobilized animals and the causal mechanisms of such changes must be identified as an essential part of this assessment. The possible influence of body position should be determined, and data should be obtained on whether there is a threshold level of whole body or partial body hypokinesia for generation of pathologic effects in the heart.

3. Suggested Research

Research protocols for confirming the preliminary data on histopathologic changes in the cardiovascular systems of immobilized animals should, if possible, be designed to differentiate between the influence of immobilization versus that of the body posture used to simulate zero-G; that is, to eliminate, if possible, the stressful effects of the restraint system. Otherwise, data from such studies may prove invalid for evaluating the effects of simulated weightlessness (Burton et al., 1981).

Among the items that should be included in studies of the myocardium are (a) the ionized calcium fluxes across the myocardial cell membranes, (b) circulating levels of CPK myocardial isoenzymes, (c) the serum transaminases, and (d) changes in myocardial hydroxyproline content. As mentioned above, improved, noninvasive methods for measuring cardiac mass and volume should be developed. Three-dimensional echocardiography, currently somewhat developmental, may ultimately prove a superior method, as may the DSR, (see p.29).

The semi-isolated papillary muscle technic is said to be advantageous for certain types of experiments on myocardial function and metabolism. For instance, the in vivo papillary muscle in an excised dog heart is perfused with arterial blood from a support dog in a physiologic manner at normal temperature. The metabolic support and its experimental perturbations will be quite analogous to natural situations. Dogs' and monkeys' papillary muscles can be studied because there is no need for the muscles to be thin as in the case of excised, diffusion-supported papillary muscle preparations (Suga et al., 1977).

Experts agree that rats are the least desirable models for such studies, rabbits are more sensitive models, and monkeys are probably best. However, the quest for a more suitable animal model should not be abandoned. Members of the Working Group favored the continued use of bed rest and other ground-based methods of simulation in studies designed to detect possible changes in ventricular mass of animal and human subjects.

D. HORMONAL AND NEUROHUMORAL FACTORS

1. Current Status

The possible relationships of the observed changes in circulating and excreted levels of certain hormones to cardiovascular adaptation and deconditioning during actual or simulated weightlessness are poorly understood. Other hormones and tissue regulators may also be affected by zero-G such as testosterone, pituitary growth hormone, and the insulin-like growth factors. The negative nitrogen and calcium balances associated with space flight are of related interest with respect to myocardial as well as musculo-skeletal function. In addition to the suggested research on neurohumoral and hormonal aspects of cardiovascular deconditioning (see p.35),the Working Group took note of the current and planned NASA studies of the hormonal aspects of bone mineral loss, muscular atrophy, and changes in fluid and electrolyte homeostasis resulting from spaceflight.

2. Critical Questions

It is essential to establish the practical significance of changes that have been documented in levels of circulating and excreted hormones and whether such changes exert any influence on the function of the cardiovascular system during and after weightlessness. Are the humoral changes triggered by fluid shifts? Does gravity exert a direct effect on biochemical processes?

The two- to four-fold increase of insulin levels in human subjects during bed rest studies raises the questions of whether this occurs in weightlessness and what is its practical meaning. Does the simulated zero-G result in the release of a blocking agent? What is the influence of an apparent increase in insulin resistance on the metabolism of the heart and blood vessels?

One task in the NASA research program on cardiovascular deconditioning involves investigation of the effects of sustained cephalad fluid shifts on the pressure and composition of CSF. An associated question concerns possible functional changes in the pituitary portal system as a result of enduring increases in jugular vein pressure during weightlessness.

In view of the tendency toward decreased secretion of ADH during spaceflight, the possible influence of this hormone on the function of cardiovascular baroreceptors assumes added interest.

3. Suggested Research

Insulin resistance associated with actual and simulated weightlessness should be quantified. The temporal changes in serum hormone levels should be analyzed during both simulated and actual weightlessness. Substances that should be measured include, but are not limited to, insulin, glucagon, T_3, T_4, renin, aldosterone, vasopressin, circulating myocardial CPK isoenzymes, and fatty acids. The Working Group supports the plan for determining renin, aldosterone, and vasopressin levels in members of Shuttle crews in future missions.

A simple glucose tolerance test, along with serum insulin levels, could be performed in crew members during future missions. In experimental animals, the sensitivity of glucose transport (or transport of non-metabolized sugars) to stimulation by insulin could be determined on isolated muscle preparations.

Preliminary findings suggest the presence of a potent antidiuretic substance (atrial factor) in the atria of rats (DeBold, 1981; Sonnenberg et al., 1981). This line of investigation appears to be of potential interest in cardiovascular-renal regulation.

E. COUNTERMEASURES

1. Current Status

The Working Group recognizes the great practical importance of developing efficient and effective methods of countering the untoward effects of cardiovascular adaptation to zero-G. Currently available methods, including exercise, periodic exposure to LBNP, rehydration, drugs, the anti-G suit, and combinations of these methods require additional test and development for confirmation of their practical utility.

The value of exercise for the prevention of cardiovascular deconditioning has not been adequately documented. Nevertheless, some data and considerable expert opinion suggest that exercise has merit as a countermeasure. With regard to drugs, in bed-rested volunteers subjected to 60° head-up tilt, the beta-adrenergic blocker, propanolol, reduced tachycardia, prevented a fall in arterial pressures, and abolished the tilt-induced fall in systemic vascular resistance (Melada et al., 1975). A calcium antagonist has been shown to exert a favorable influence on hemodynamics in subjects deconditioned by hypokinesia (Bogolyubov et al., 1978).

2. Critical Questions

Knowledge of the potential of periodic exposures to LBNP as a means of prophylaxis against certain components of cardiovascular deconditioning is insufficient to determine whether this approach would be a good countermeasure. What frequency and duration of application of LBNP would be most effective? Is it necessary to place the entire lower half of the body in a vacuum or would lower extremities suffice? What is the most practical means of providing LBNP for spacecrews?

Similarly, how effective is muscular exercise as a countermeasure? Questions of the best types, patterns, and schedules of exercise for enhancing homeostasis of the cardiovascular, musculoskeletal, and other organ systems and functions require further investigation. For instance, inflight muscular exercise should help to maintain Earth-equivalent cardiovascular function if it is extensive enough to match the workload that prevails at 1-G. Have estimates been made of the magnitude of the reduced workload that results from weightlessness?

Is it desirable to maintain tone of the abdominal muscles in order to help control pooling of blood in the abdomen and possibly increase cerebral blood flow? There is some experimental evidence to support the latter concept (Heite and Lerche, 1939), but not the former (Howard, 1965). If future data indicate that exercise improves the astronaut's ability to cope with inflight and postflight effects of cardiovascular adaptation and deconditioning, what are the optimum amounts and schedules?

What is the evidence that anti-G suits provide significant antiorthostatic protection for astronauts during reentry in the Shuttle Orbiter at positive accelerations of $<2\ G_Z$? Some data, in bed-rested subjects, show that the anti-G suit protects against orthostatic intolerance (Miller et al., 1964a,b) and preserves $+G_Z$ acceleration tolerance (Chambers and Vykukal, 1972; Jacobson, et al., 1973). However, a question persists as to whether an operational need exists for anti-G suits during reentry of the Shuttle Orbiter (see p.29). In addition, the functional significance of possible changes in human intrapulmonary and cardiac morphology and performance during use of the anti-G suit is unknown.

Drugs may offer some additional means of coping with certain aspects of cardiovascular deconditioning. More information is needed on the value of pressor agents and of atropine in orthostatic intolerance.

3. Suggested Research

The possible utility of LBNP or other methods of influencing hemodynamics in the lower extremities deserves further study. If data from future ground-based investigations indicate that such technics exert a favorable effect on cardiovascular deconditioning, additional investigations should be planned to determine optimum methods and minimum effective schedules, and then tested inflight. The question of whether LBNP should be combined with other countermeasures, such as fluid and electrolyte repletion, should also be investigated. If the experimental results of LBNP or its variants are encouraging, a vigorous developmental effort should be programmed for an optimum means of providing LBNP to spacecrews.

Alternate means to LBNP for "hemodynamic exercising" of the lower extremities during weightlessness are needed. For example, the feasibility and effectiveness of inducing intravascular pressure surges in the thighs and legs by repeated abrupt decelerations in the $+G_Z$ axis, such as may occur with a trampoline-type device (Chase et al., 1966) or a mechanically-driven, whole body oscillator (Bhattacharya et al., 1979) might be reassessed as possible models for countermeasures. The value of using a combination of a reverse pressure-gradient garment and such an exercise technic should be considered.

Studies of drug intervention against aspects of cardiovascular deconditioning should be encouraged not only for development of countermeasures but also as an approach toward explaining basic mechanisms. For instance, the myocardial damage reported in monkeys immobilized for several months may be prevented or modified by certain drugs, such as β-blockers.

Further studies are indicated on the utility of available anti-G suits for reentry protection in the Shuttle Orbiter as well as for postflight use. The possibility of improving the fitting of the anti-G suit to compensate for the marked reduction of leg volume of astronauts inflight should be explored. In addition, further studies are needed to determine the practical effectiveness and need for the anti-G suit for exposures of 1.5 to 2.0 $+G_Z$ for periods of 20 to 30 minutes (see p.29). With respect to a possible need for lower body positive pressure support postflight, a recent report on the hemodynamic effects of medical anti-shock trousers is noteworthy (Gaffney et al., 1981).

Similarly, in view of its documented efficacy as an anti-orthostatic aid in short-term exposures to higher levels of $+G_Z$, the possible need for and feasibility of positive pressure breathing capability during reentry of the Shuttle Orbiter should be assessed (Rutishauser et al., 1966) (see also p.29). In addition, current studies to evaluate body cooling as a means of resisting orthostatic intolerance during reentry and postflight may yield sufficiently promising results to warrant further consideration.

F. METHODOLOGY

1. Current Status

Identification of physiological mechanisms underlying cardiovascular deconditioning requires accurate measures of cardiac output, central venous pressure, dynamic heart chamber volumes, and blood, plasma, and interstitial volumes. Thus, there is a need for more accurate methods for measuring these critical variables with less invasive technics than were heretofore available. NASA strives to keep abreast of advances in instrumentation and methodology that may be applicable to investigations of the biomedical problems of space flight.

A majority of the members of the Working Group regarded use of available ground-based models and a search for ways to improve them as essential for progress in this field. Because of reasons described on page 10, one member of the Working Group was skeptical of the fidelity of ground-based models as a means of studying the mechanisms of cardiovascular deconditioning associated with weightlessness.

The Working Group supported the general principle that, whenever possible, measurements made in ground-based experiments should be confirmed inflight, preferably in the same subjects. Adherence to such a principle would aid in assessing the validity of both animal and human data obtained from ground-based studies. However, it is NASA's policy to reserve opportunities for inflight observations only for acquiring data that cannot be obtained in ground-based facilities. In addition, the Working Group noted the importance of using the best available models for animal studies and the need for seeking better animal models. In general, animals sufficiently large to exhibit hemodynamic responses that are similar to the human responses to simulated weightlessness are preferable for studying cardiovascular deconditioning.

With respect to computer models of the cardiovascular system in the weightless or bed-rest environments, the Working Group considered the present state of knowledge of mechanisms of cardiovascular deconditioning inadequate for development of complex interactive models that could, for instance, predict an astronaut's cardiovascular responses during various stages of a space mission. However, incomplete, tentative models can serve useful functions by revealing deficiencies in knowledge, indicating specific data to be obtained, and assigning some order of priority for procuring data.

2. Critical Questions

Important questions pertain to the subject of simulating weightlessness, such as how valuable are currently-used

ground-based models and how closely do they simulate actual space flight? Should other environmental factors of space flight, such as confinement in spacecraft mock-ups, use of spacecraft type environmental control systems, social isolation, and altered light-dark cycles, be designed into ground-based models? Do the reflex circulatory responses associated with pressure on the skin significantly influence bed rest as a suitable model (Takagi, 1960)?*

Use of a model of the cardiovascular system may improve experimental design by indicating the need to include many factors and the interactions among them, and might address such questions as the explicit expression of our understanding of the interrelationships of all the major factors involved in cardiovascular deconditioning. To what extent are the cardiovascular changes accounted for by blood volume changes? How much blood volume repletion is desirable? How much of a role do baroreceptors play? How much do changes in venous compliance or capacity influence cardiovascular responses?

Finally, a question arose regarding the value of studying animals immobilized for long periods. It was considered that the associated psychological stress might invalidate such models for the study of cardiovascular deconditioning (Burton et al., 1981).

3. Suggested Research

The Working Group stressed the need for improving methods for both direct and indirect measurements of cardiovascular parameters that are essential in NASA's investigations, and emphasized standardization of methodology as an aid to acquisition of compatible, reproducible data and to minimize some experimental variables. Functions and characteristics of the cardiovascular system for which improved methodology is needed for use in living subjects in actual and simulated zero-G include: myocardial mass, heart chamber volumes, cardiopulmonary dimensions, absolute changes in venous volumes and capacitance, plasma volumes, interstitial and total body water, and the densities and sensitivities of the mechanical, chemical, and neurohumoral cardiovascular receptors.

An example of a type of instrumentation development that is of interest to NASA is that of J.D. Hestenes (O'Handley, 1982) on a method of extracting physiologic features from cardiac and arterial ultrasound images. J. Hines and H. Sandler (Sandler, 1982b) are miniaturizing, repackaging, or redesigning already

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* Additional references on circulatory responses to skin pressure may be obtained from Dr. Sagawa whose full name and address are listed in Section VIII.

available biotelemetry systems for use in small laboratory animals, for space flight studies. A third example is the work of J.L. Lacy (Bungo, 1982) to improve cardiac imaging by means of tantalum 178, a radionuclide that offers certain advantages over other radioisotopes used in cardiac imaging, such as a relatively short radioactive half-life.

Efforts should be continued to evaluate the efficacy of and to improve ground-based models of weightlessness. Attempts should be made to assess the effects of gravity-induced pressure gradients and associated blood volume and flow throughout the systemic and pulmonary circulations on the validity of bed rest as a model of weightlessness. In designing and interpreting experiments on the effects of simulated weightlessness and hypokinesia, investigators should bear in mind that physiologic changes evoked by otherwise unrestrained resting conditions may differ from those elicited by immobilization.

With respect to computer models, the Working Group suggested that incomplete, tentative models theoretically would be helpful to investigators, as mentioned above. For example, the models described by Snyder and Rideout (1969), which incorporated gravitational force, and Shoukas and Sagawa (1973), which distinguished between compliance and capacity, could be useful. In addition, the models described by Guyton et al. (1972), Coleman et al. (1974), Randall (1980), and Rothe (1982) could be helpful. A modeling program that has yielded interesting results in relation to biomedical effects of space flight is based upon Guyton's original model (Guyton et al., 1972) and other models of the circulation. It involves a systems approach to defining human responses to the environment of space flight and to the formulation and testing of associated hypotheses (White et al., 1982).

The current model of "Human-80" is probably the most sophisticated model now available of the human body in health, disease, and during treatment. Cardiovascular, respiratory, renal, endocrine, and reflex factors are included. It is based on Guyton's model described in 1972, has 479 variables, yet can be run on a microcomputer as well as on larger systems.* Any model would have to be modified to simulate the effects of weightlessness, but this extensively used and sophisticated model would provide a good foundation.

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* Dr. James Randall (Department of Physiology and Biophysics, Myers Hall, Indiana University, Bloomington, IN 47405) or Dr. Thomas G. Coleman (Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS 39216) could provide further information.

VI. PROPOSED PRIORITIES OF SUGGESTED RESEARCH AND ANALYSIS

The main objective of the NASA ground-based research and analysis program in cardiovascular deconditioning is the acquisition of scientific data that will lead to practical methods of prevention or control of the syndrome. The current lack of adequate data indicates clearly the continuing need for investigations focusing on the biological mechanisms involved and improvement of technics, methods, equipment, and facilities to further such endeavors.

The research and analysis concepts listed in Table 6 were derived from the deliberations of the ad hoc Working Group. The categories in Table 6 are interrelated and were all considered as important programmatic components; however, within the six separate categories, the suggestions for research emphasis are presented in a decreasing order of priority.

In addition, the Working Group recognizes the need for unequivocal confirmation of the methodologic suitability of the currently-used or alternate ground-based models of the space flight environment, particularly with respect to weightlessness. The fundamental importance of this question may justify its formal treatment as a distinct program element with designated managerial responsibility. Finally, the untoward effects on cardiovascular system function that have been observed during the first days and weeks immediately following long space missions, the lack of knowledge of the underlying biologic mechanisms involved, and the unproved efficacy of currently available countermeasures all emphasize that solution of the problem of cardiovascular deconditioning justifies a high priority within NASA research and technology programs.*

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* One member of the LSRO ad hoc Working Group suggested that this section required altered emphasis (see Appendix, p.67-69).

Table 6. Suggested Priority of NASA Ground-Based Research and Development in Cardiovascular Deconditioning*

A. HEMODYNAMICS

- Assess cardiovascular function, using multiple end points, at selected stages of simulated space missions, including the first 24 hours.
- Determine whether cardiac filling pressure increases or decreases in simulated weightlessness and characterize its time course.
- Characterize changes induced by simulated weightlessness on cardiopulmonary blood pressure relationships and their influence on cardiovascular deconditioning.
- Measure changes in total vascular capacitance in human and animal models of cardiovascular deconditioning.
- Determine changes in regional systemic and pulmonary blood volumes and blood flows and their effects on cardiovascular functional capacity in a model of deconditioning.
- Determine whether intraabdominal pressure changes occur in simulated weightlessness and whether abdominal muscle tone influences hemodynamics.
- In ground-based studies, determine the operating point of the heart in relation to the Frank-Starling curve.

B. ENDOCRINE AND NEUROHUMORAL ASPECTS

- Formulate experiments to detect the effect on cardiovascular system function associated with changes in levels of circulating and excreted hormones that have been observed in real and simulated weightlessness.
- Perform detailed, serial analyses of temporal changes in serum hormone levels in bed-rested subjects during simulated space missions. Candidate substances should include insulin, glucagon, catecholamines, T_3, T_4, renin, aldosterone, vasopressin, myocardial CPK isoenzymes, fatty acids, cholesterol, and high- and low-density lipoproteins.

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* Listed in suggested decreasing order of priority within each of six separate categories. See Section V, A-F for detail.

Table 6 (continued)

- Study the influence of atrial and ventricular sensory receptors on regulation of cardiovascular function and on release of vasopressin and aldosterone in simulated weightlessness.

- Further define and quantify insulin resistance associated with simulated weightlessness.

- Measure changes in intracranial vascular and cerebrospinal fluid (CSF) pressures associated with simulated zero-G. Correlate the changes with alterations in CSF composition, pituitary portal system function, and regulation of the cardiovascular system.

- Study the functional relationship between vasopressin and cardiovascular system baroreceptors.

- Design experiments to differentiate between hypokinesia and simulated weightlessness in the induction of hormonal changes associated with space flight.

- Study the effects of elevated or depressed catecholamine concentrations on adrenergic receptor density and sensitivity in the cardiovascular system if significant variation in circulating levels of catecholamines can be induced in a model of deconditioning.

C. MYOCARDIAL CHANGES

- Characterize the myocardial changes that have been reported in chronically immobilized animals. Identify temporal aspects and specific etiologic factors.

- In studying the effects of simulated weightlessness on the heart, consider measuring changes in: (a) ionized calcium fluxes across the myocardial cell membrane, (b) circulating levels of CPK myocardial isoenzymes, and (c) myocardial hydroxyproline content.

- Differentiate between the myocardial and hemodynamic effects of immobilization versus postural, immersion, or other methods of simulating zero-G in animal models of cardiovascular deconditioning.

D. RELATED FACTORS

- Locate the sites of possible defects in reflex control of the circulation that contribute to cardiovascular deconditioning.

Table 6 (continued)

- Assess the relative importance of high- and low-pressure baroreceptors in the reflex control of the circulation during and after weightlessness.
- Determine in an animal model of cardiovascular deconditioning whether changes occur in the density and sensitivity of the cardiovascular adrenergic receptors in response to simulated weightlessness.
- Determine the relative importance of physical inactivity dictated by the spacecraft dimensions and personal protective equipment versus weightlessness in the induction of cardiovascular deconditioning.
- Study the relationship between end-systolic volume of the heart and vaso-vagal syncope as an approach to identifying the "trigger" mechanism of syncope.
- Conduct studies of human subjects during bed rest in order to investigate the functional changes in baroreceptors.

E. METHODS, EQUIPMENT, AND FACILITIES

- Improve the methods of measuring in living subjects such characteristics as cardiopulmonary dimensions, heart chamber volumes, myocardial mass, plasma volumes, erythrocyte mass, and interstitial and total body water.
- Design experiments with LBNP coupled with measurement of atrial and ventricular pressures in order to study the role of associated mechanoreceptors in cardiovascular function. LBNP activates low-pressure receptors and neck suction activates the high-pressure receptors.
- Refine the methods of measuring baroreceptor function, per se, in conscious subjects.
- Assess the influence of gravity-induced pressure gradients throughout the body on the efficacy of ground-based models of weightlessness.
- Develop methods to measure absolute changes in venous volume and venous capacitance of bed-rested subjects.
- Develop a method for analysis of the responses of low-pressure baroreceptors in simulated weightlessness.

Table 6 (continued)

- Conduct further validation studies of head-down tilt bed rest as a method of simulating weightlessness.

- Assess the possible need for improving the fidelity of ground-based facilities for human studies by incorporating such items as spacecraft mockups, environmental control systems, and social isolation.

- The search for better animal models for studies of cardiovascular deconditioning should continue. Preferably, the animal should be large enough and of a morphology to have hemodynamic responses similar to human responses. Rats appear to be poor models for such studies; large monkeys and chimpanzees are probably the best yet identified.

- Encourage investigators to use models of the cardiovascular system when they design experiments on cardiovascular deconditioning, even though available knowledge of the mechanisms involved is incomplete.

F. COUNTERMEASURES

- Expand the test and development of extant types of putative countermeasures to confirm their possible efficacy and to refine their patterns and means of use. Examples of putative measures are muscular exercise, LBNP, fluid and salt repletion, and combinations of these.

- Develop alternate means for stressing the vascular system of the lower extremities during weightlessness.

- Perform tests with deconditioned subjects to determine whether the anti-G suit is a practical countermeasure to decelerative stress during Shuttle Orbiter reentry.

- Develop the means to assure precise fitting of the anti-G suit for the lower extremities of spacecrews if studies indicate that the anti-G suit offers practical reentry protection in the Shuttle Orbiter.

- Determine the optimum frequency and duration of LBNP as a prophylactic countermeasure for cardiovascular deconditioning in bed-rested subjects. Determine the minimum amount of body exposure to LBNP below the thorax that is necessary for a preventive effect.

Table 6 (continued)

- Formulate experiments to test the utility of drugs and hormones as prophylactic or therapeutic countermeasures to the orthostatic intolerance of cardiovascular deconditioning.
- Design a study of astronauts to (1) identify those who demonstrate relative resistance to cardiovascular deconditioning as may be estimated from inflight and postflight physiologic responses, and (2) to define physiologic and/or behavioral correlates of such resistance.
- Estimate the amount of muscular exercise required in spaceflight to equal the work done in selected amounts of muscular exercise on Earth. Apply findings to the design of ground-based tests of the utility of muscular exercise regimens.
- Reassess the possible need for and feasibility of using positive pressure breathing equipment in conjunction with the G-suit during reentry of the Shuttle Orbiter.
- Perform measurements in bed-rested subjects of possible changes in cardiopulmonary morphology induced by use of the anti-G suit, and estimate their significance.

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VIII. STUDY PARTICIPANTS

A. ATTENDEES, AD HOC MEETING, July 6-7, 1982

CO-CHAIRMEN

Matthew N. Levy, M.D.
Chief, Investigative Medicine
Mt. Sinai Medical Center
University Circle
Cleveland, Ohio 44106

John M. Talbot, M.D.
Senior Medical Consultant
Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20814

PARTICIPANTS

Jere H. Mitchell, M.D.
Professor of Medicine and
Physiology
University of Texas South-
western Medical School
5323 Harry Hines Blvd.
Dallas, Texas 75235

Carl F. Rothe, Ph.D.
Professor of Physiology
and Medical Biophysics
Indiana University School
of Medicine
Indianapolis, Indiana 46223

James R. Neely, Ph.D.
Professor of Physiology
Hershey Medical Center
Pennsylvania State University
Hershey, Pennsylvania 17033

Kiichi Sagawa, Ph.D.
Professor, Department of
Biomedical Engineering
Johns Hopkins University
School of Medicine
Baltimore, Maryland 21205

Earl H. Wood, M.D., Ph.D.
Professor of Physiology
and Medicine
Mayo Foundation and Graduate
School of Medicine
Rochester, Minnesota 55901

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
Washington, D.C. 20546

Paul C. Rambaut, Sc.D.
Manager, Biomedical Research Program
Life Sciences Division
Office of Space Science and Applications
NASA Headquarters
Washington, D.C. 20546

Harold Sandler, M.D.
Chief, Biomedical Research Division
Life Sciences Directorate
Ames Research Center
Moffett Field, California 94035

LIFE SCIENCES RESEARCH OFFICE

Sue Ann Anderson, Ph.D., R.D.
Staff Scientist

Kenneth D. Fisher, Ph.D.
Director, LSRO

SPECIAL REVIEWERS

Robert W. Krauss, Ph.D.
Executive Director
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20814

Orr E. Reynolds, Ph.D.
Executive Secretary-Treasurer
American Physiological Society
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20814

B. OTHER CONTRIBUTING LIFE SCIENCES RESEARCH OFFICE STAFF

Richard G. Allison, Ph.D.
Senior Staff Scientist

Philip L. Altman, M.S.
Senior Staff Scientist

Sandra Ferman
Administrative Aide

Beverly Keder
Literature Retrieval/ Technical Report Specialist

Jennette Moten
Secretary

Frederic R. Senti, Ph.D.
Associate Director, LSRO

APPENDIX

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MINORITY OPINION*

Page vii - third paragraph

"Critical questions and suggested research

Since it seems quite certain that elimination of hydrostatic gradients in the venous circulation and a consequent increase in right atrial and probably left atrial pressures caused by the resulting central ward shift of circulatory blood volume is the initiating factor of the hemodynamic effects of zero gravity it is of highest priority to obtain measurements of right atrial pressures during and after the onset of the zero-G environment.

Without information concerning the magnitude and time course of these presumed changes in right atrial pressure the significance relative to space flight of ground-based models which do not produce closely similar changes cannot be assessed.

Other considerations deserving high priority include: (1) whether degenerative changes occur in the cardiovascular system during medium- and long-term missions, in particular, a possible loss of myocardial mass, (2) the nature and temporal development of changes in cardiovascular regulatory control mechanisms, (3) possible changes in the density and sensitivity of the pressure, volume, and neurohumoral receptors in the cardiovascular system, (4) alterations in vascular compliance and capacity, (5) associated changes in hemodynamics, and (6) the nature of the redistributed blood flows."

Page 10 - third paragraph should read as follows:

"The serious deficiencies of earth based models of the zero gravity environment are generally over looked or minimized. They are however of such magnitude that the relevance of observations using these models to the zero gravity situation is at best open to serious question and, at worse, of no practical significance relative to space flight.

It is true that a partial shift of blood volume from the lower extremities headward can be produced by water immersion and by the horizontal or 5° head down position. However, this is not an adequate simulation of the zero G condition.

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* The text and references of the Minority Opinion are presented as submitted, without editing (M.N.L., J.M.T.).

This is because no currently conceivable stationary earth based model can mimic the multiple other important effects of zero-G resulting from the absence of the affects of gravity on:

1) The spatial distribution of pulmonary blood volume and flow particularly in the vertical direction (1-4) as well as dependent hydrostatic capillary filtration. All of which, because of the approximately 15-20 cm transverse diameters of the lungs as compared to the 20-30 cephalo-caudad dimension, are only moderately reduced in the horizontal position at 1 G and are unchanged during head-up water immersion.

2) The dimensions, shape and position of the diaphragm and thoracic cage, i.e. lung volume (5).

3) The shape and positon of the heart and its chambers.

4) The spatial distributions, particularly the vertical gradient, in atrial and ventricular transmural pressures which differ in direction but are of similar magnitude irrespective of body position at 1 G (6-8).

5) The spatial distribution of respiratory gas volumes and flows particularly in the vertical direction (9, 10).

6) The spatial distribution, particularly the vertical gradient, in pleural pressures which is present to a significant degree in all body positions (11-18).

7) Pooling of blood and increased hydrostatic capillary filtration in dependent regions of the systemic vasculature which, because of the 5-25 cm transverse dimensions of the human body, are significant even in the horizontal position.

8) The vertical gradient in intra-abdominal pressures which is present to a significant degree in all body positions (19, 21).

9) The vertical gradient in cerebrospinal fluid pressures which is also present to a significant degree in all earth-bound body positions.

This list of deficiencies of all currently conceivable stationary earth based models of zero gravity is arranged in descending order relative to their probable hemodynamic significance.

This hierarchical arrangement stems from the fact that the effects of gravity on the spatial distribution of pulmonary blood and gas volumes and flow, position of the heart and diaphragm, and dependent (hydrostatic) pulmonary pooling and capillary filtration cannot be avoided by either bed rest or water immersion. These effects of gravity on the heart, lungs and great vessels are probably of major importance in the adaptation of humans to the 1 G force environment of planet earth. This is because the heart, lungs, and great vessels are the most compliant segments of the vascular system, and hence are the major recipients

of a zero G medicated cephalad shift in blood volume. In addition, unlike zero gravity, the volume of the thoracic cavity is reduced by upward displacement of the diaphragm during either water immersion or bed rest. These multiple differences highlight the fact that all currently conceivable earth-bound models fail to simulate many of the majorly important hemodynamic and pulmonary aspects of the agravic environment.

Use of animal models as surrogates for unanesthetized humans relative to the effects of changes in the magnitude and/or the direction of the gravitational-inertial force environment is equally discouraging in relation to obtaining practically important information relative to human space flight problems (20).

Just as proved to be the case relative to studies of the $+G_z$ black-out problem during World War II, it is likely that none or at best only a very limited category of results from animal studies will prove to be of practical importance to human space flight. Furthermore it is possible, as occurred during World War II, that results from animal studies may actually be misleading relative to human flight problems (21, 22).

Since bodily dimensions are of primary importance relative to susceptability to changes in the force environment (e.g. mice can survive exposures to 400 G) the bodily dimensions and shape, particularly of the thorax, of animal surrogates should be closely similar to humans.

These considerations lead to the conclusion that NASA's research program to elucidate zero G induced cardiovascular deconditioning should be focused primarily on the stimulation and support of studies which carry the highest potential of obtaining quantitative accurate measurements in humans of the changes in the most important physiologic parameters relative to the acute and chronic hemodynamic and resulting associated effects of space flight. This essential information is at present either missing or not well documented.

The essential missing information relative to the magnitude and time course of the hemodynamic effects of the zero G environment in order of importance are:

> 1) right atrial pressures, 2) the magnitudes and spatial distributions of pulmonary blood and gas volumes and flows, 3) the associated changes in left atrial pressures, 4) position, shape and pressure-volume dynamics of the cardiac chambers, 5) shape and position of the diaphragm and associated lung volumes, 6) possible changes in myocardial mass.

It is highly probable that, except for psychological and psychosomatic factors, most or all of the other effects of the zero G environment on the heart, lungs, circulation, body fluids electrolytes and related neurohumoral

changes are initiated by the absence of hydrostatic circulatory, body fluid and tissue pressure gradients which pertains at the onset and for the duration of space flight.

It is therefore of primary importance that the effects of the absence of hydrostatic pressure gradients particularly in the most mobile organ of the body, i.e. the blood and its effects on the major segments of the circulatory system, be measured accurately, and as non-invasively as possible, in healthy humans at the onset and during space flight along with essential control measurements just prior to and after the zero G exposure.

Certainly definitive studies of these effects of microgravity in man as well as large animals will require accurate minimally invasive measurements of atrial filling pressures along with cardiac chamber volume dynamics, myocardial mass, spatial distributions and magnitudes of systemic, pulmonary and coronary blood volumes and flows plus the shape and position of the diaphragm and the associated spatial distributions and the magnitudes of pulmonary gas volumes and flows (ventilation).

High speed, accurate three dimensional reconstruction of the dynamic anatomy and the resulting synchronous functional dynamics of these organ systems which can be obtained by high speed synchronous volumetric scanning tomography is the only currently conceivable system which will provide the unique capabilities required for making accurate, minimally invasive, synchronous measurements of these parameters in intact animals and humans (23-27)."

Page 10 - suggest fourth paragraph read as follows:

"Blomqvist and Stone (1983) note that a marked change in the hydrostatic conditions that prevail in the systemic circulation in humans in the upright positions on Earth results when subjects are exposed either to experimental bed rest and to head-out immersion in water. However, the inability to duplicate the complete absence of all hydrostatic effects in all tissues and segments of the circulation, particularly and very importantly within the thorax, which pertains at zero-G is a serious deficiency of all stationary ground based models. A redistribution of intravascular and interstitial fluid from the lower to the upper half of the body is one of the major, acute, hemodynamic effects of both zero-G and its ground based models. Presumably therefore the mechanisms for adaptation to the relocated fluids and altered intravascular pressures associated with bed rest, and water immersion, may be similar to the effects of zero G. In any event, hypovolemia, reduced stroke volume and cardiac output, orthostatic intolerance, and decreased exercise capacity are the common results of exposure to real and simulated weightlessness (Blomqvist and Stone, 1983)."

Page 41 - the following should be added after the last paragraph:

"A suggested set of efforts listed in order of priority for a NASA research and development program designed to elucidate the mechanisms and methods for prevention of the cardiovascular deconditioning associated with exposures to zero G follows:

1) It is an accepted fact that a cephalad shift of blood volume occurs uniformly at the onset of exposures to zero G. It is also suspected but not firmly documented that an increase in right atrial filling pressure occurs at this time.

   Since this is the initial major hemodynamic effect of exposure to zero G and is probably responsible for most or many of the changes which are responsible for the cardiovascular deconditioning which follows, it is of critical importance and of highest priority that accurate measurements of the magnitude and the time course of changes in right atrial pressures be obtained beginning as soon as possible after the onset of zero G.

2) Since accurate studies of these effects would be greatly facilitated if the hemodynamic effects of zero gravity could be faithfully simulated in a ground based environment it is of next highest priority to determine if closely similar changes in the magnitude and time course of possible changes in right atrial filling pressures occur in the most frequently used ground based simulations of weightlessness namely: horizontal bed rest, 5° head-down bed rest, and water immersion to the neck. If closely similar changes in right atrial filling pressure do not occur under these circumstances the pertinence of results of studies of these ground based models relative to the hemodynamic, pulmonary and subsequent effects of zero gravity may be close to zero.

3) Since quite certainly the cephalad shift in blood volume at the onset of an exposure to zero gravity is associated with: 1) changes in position, shape, dimensions, and pressure-volume dynamics of the cardiac chambers and

2) changes in the magnitudes, and spatial distributions of pulmonary blood and gas volumes and flows and 3) the shape, position of the diaphragm and thoracic cage with the resultant changes in regional and total lung volumes, and at present there are no accurate technics for minimally invasive measurements of these parameters in intact large animals or humans, it is of next highest priority to develop adequate instrumentation and techniques to obtain these measurements. The number 3 priority rank of this task holds irrespective of the outcome of priority 1 and 2 tasks.

The only known method with the capabilities of minimally invasive, nearly simultaneous measurements of this battery of physiologic parameters is the technic of non-invasive vivisection of quantitative, dynamic, three dimensional images of the thorax and its contents obtained by high speed synchronous volumetric scanning tomography (23-32).

4) Utilize these and associated measurement technics to determine the probable significance of the differences in the hemodynamic and pulmonary effects produced by zero G and the most commonly used methods for ground based simulations of the space flight environment.

5) Utilize these same measurement technics to study the mechanisms and the effectiveness of various counter measures to the zero G environment particulary LBNP and exercise.

6) Because of the probability and some evidence that 20 minute exposures to 1.5-2.0 $+G_z$ during reentry from space shuttle flights may interfere with astronaut performance, studies of the hemodynamic and possible associated CNS effects of approximately 20 minute exposures to 1.5-2.0 $+G_z$ in seated healthy humans should be carried out before and after bed rest.

The use of a photoelectric earpiece and associated circuitry for continuous simultaneous recordings of the blood content of the ear, the ear opacity pulse and arterial oxygen saturation for non-invasive monitoring of the subjects hemodynamic status should be investigated (33-35) along with ultrasonic methods for detection of temporal artery flow (36).

It would be of considerable physiologic and also of practical value to obtain recordings of these parameters in three types of exposures in random sequence: a control relaxed exposure, and exposure with a G suit inflated to about 40 mm Hg, and an exposure with the G suit inflated while pressure breathing at a moderate level of about 20 mm Hg.

It would also be of considerable additional value to carry out these exposures when breathing air and when breathing 100% oxygen with chest roentgenograms before and immediately after the exposures, to study the probable occurrence of dependent atelectasis during such exposures (34) and associated pulmonary arteriovenous shunts for correlation with possible ear oximeter arterial saturation changes (14-16)."

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1. Report No.	2. Government Accession No.	3. Recipient's Catalog No.
NASA CR-3707		

4. Title and Subtitle	5. Report Date
RESEARCH OPPORTUNITIES IN CARDIOVASCULAR DECONDITIONING - FINAL REPORT PHASE I	July 1983
	6. Performing Organization Code
7. Author(s)	8. Performing Organization Report No.
M. N. Levy and J. M. Talbot, Editors	
	10. Work Unit No.
9. Performing Organization Name and Address	11. Contract or Grant No.
Life Sciences Division, Federation of American Societies for Experimental Biology, 9650 Rockville Pike, Bethesda, MD 20814	NASW-3616
	13. Type of Report and Period Covered
12. Sponsoring Agency Name and Address	Contractor Report
National Aeronautics and Space Administration Washington, D.C. 20546	14. Sponsoring Agency Code EBT

15. Supplementary Notes

NASA Technical Monitor: Paul C. Rambaut

16. Abstract

This report contains a summary review of the deconditioning of the cardiovascular system that occurs during spaceflight, comment on NASA's current and projected research program, and the conclusions and suggestions of the ad hoc Working Group.

17. Key Words (Suggested by Author(s))	18. Distribution Statement
Spaceflight, Cardiovascular	Unclassified - Unlimited
	Subject Category 52

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	72	A04

For sale by the National Technical Information Service, Springfield, Virginia 22161 NASA-Langley, 1983